Structure−Activity Studies and Analgesic Efficacy of *N*-(3-Pyridinyl)-Bridged Bicyclic Diamines, Exceptionally Potent Agonists at Nicotinic Acetylcholine Receptors

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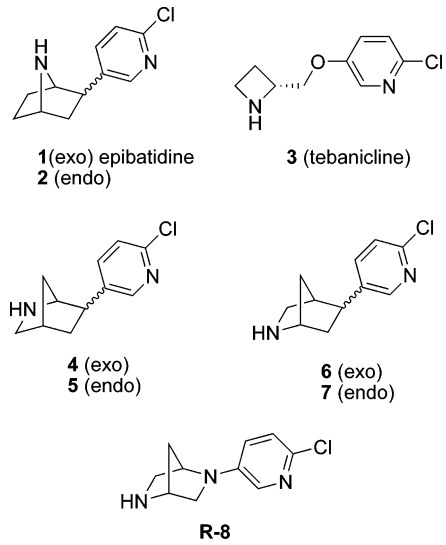
A series of exceptionally potent agonists at neuronal nicotinic acetylcholine receptors (nAChRs) has been investigated. Several *N*-(3-pyridinyl) derivatives of bridged bicyclic diamines exhibit double-digit-picomolar binding affinities for the α4β2 subtype, placing them with epibatidine among the most potent nAChR ligands described to date. Structure−activity studies have revealed that substitutions, particularly hydrophilic groups in the pyridine 5-position, differentially modulate the agonist activity at ganglionic vs central nAChR subtypes, so that improved subtype selectivity can be demonstrated *in vitro*. Analgesic efficacy has been achieved across a broad range of pain states, including rodent models of acute thermal nociception, persistent pain, and neuropathic allodynia. Unfortunately, the hydrophilic pyridine substituents that were shown to enhance agonist selectivity for central nAChRs *in vitro* tend to limit CNS penetration *in vivo*, so that analgesic efficacy with an improved therapeutic window was not realized with those compounds.

Introduction

Over the past decade, neuronal nicotinic acetylcholine receptors (nAChRs) have emerged as important targets for drug discovery. nAChR ligands have been proposed for treatment of Alzheimer's Disease, Parkinson's Disease, Tourette's Syndrome, schizophrenia, and other CNS disorders.[1−5] Moreover, the profound analgesic effect of epibatidine (**1**)[6] (Scheme 1) emphatically illustrates the potential of nAChR ligands as alternatives to opioids for the treatment of severe pain states.[7] Epibatidine, however, is much too toxic to be considered for clinical use. Consequently, much effort has been directed toward the discovery of new nAChR-based analgesics with improved safety profiles. The underlying rationale for this approach is the existence of a large and diverse family of neuronal nAChR subtypes, and the hypothesis that ligands that selectively act at specific subtypes will mediate analgesia with diminished liability for side effects. While the exact physiological roles of different subtypes are only beginning to be sorted out, a strong body of evidence has accumulated to indicate that central α4β2 nAChRs play a key role in the antinociceptive effects of nicotinic agonists.[8,9] Similarly, the prevalence of α3β4*-containing nAChRs in the autonomic ganglia supports the hypothesis that activation of this subtype contributes to gastrointestinal and cardiovascular adverse effects of nonselective compounds like epibatidine.[10] For example, **3** (Tebanicline), a nicotinic agonist with enhanced selectivity for activation of the α4β2 subtype compared to other nAChRs, also exhibits an improved therapeutic profile in animal models compared to epibatidine,[11] and has been advanced to human clinical trials for treatment of pain.[12] It has been reported that analgesic efficacy was established for **3** across multiple pain conditions in humans, providing clinical proof of concept for the nAChR pharmacology, but dose-limiting GI side effects prevented further development of this compound.[13] Meanwhile, medicinal chemistry efforts targeted more highly selective agonists at the α4β2 nAChR toward the goal of identifying an analgesic with improved therapeutic index. We have discovered a family of bridged-diamine based nAChR ligands with potent agonist activity and describe here structure−activity relationships and *in vivo* characterization.

Scheme 1



Among the most potent nAChR ligands discovered to date, epibatidine (**1**) binds to α4β2 receptors in rat brain with affinity in the picomolar range. The syn disposition of the pyridine to the imino bridge is crucial for the high potency of **1**, since the binding affinity of *endo*-epibatidine (**2**) is attenuated nearly 200-fold.[14] A similar difference is seen in the 2-aza epibatidine analogues recently reported by Malpass[15,16] and Hodgsen.[17] Epimers **5** and **7** with the pyridine ring proximal to the basic nitrogen are virtually equipotent to epibatidine, but the exo

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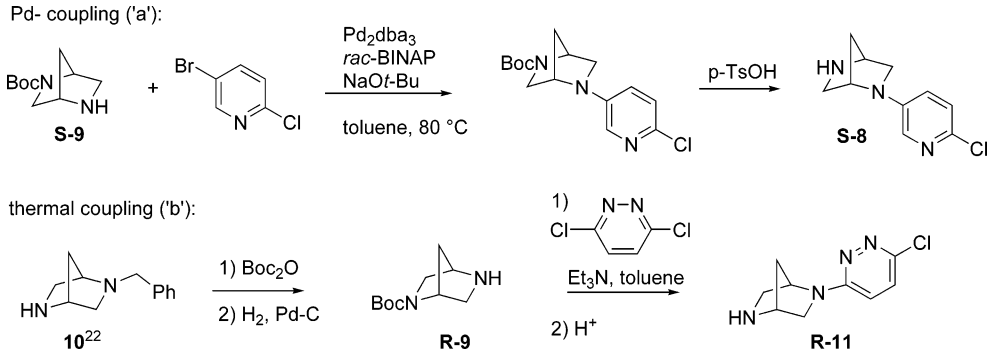
Scheme 2. General Methods for Heteroaryl−Amine Coupling



epimers **4** and **6** are several hundred-fold weaker.[15] An interesting variant is represented by compound **R-8**, in which the critical stereogenic center is eliminated by replacement of nitrogen for carbon. We have investigated this series of diamine analogues and report here that these compounds are also exceptionally potent nAChR ligands with good analgesic activity *in vivo*.

Chemistry. The nAChR ligands were prepared by condensation of a monoprotected diamine with a heteroaryl halide (Scheme 2). Halides that are activated toward nucleophilic aromatic substitution were coupled efficiently with base in refluxing toluene (Scheme 2, 'b'), but more generally the amination was accomplished using the Pd-mediated procedures developed by Buchwald and Hartwig (Scheme 2, 'a').[18,19] A variety of substituents, including alkyl, alkoxy, cyano, and nitro, can be brought in on the hetereocycle, and standard manipulation (post coupling) of these provides for a wider range of substituent effects for development of structure−activity relationships. Amination of 5-bromo-2-chloropyridine under our standard conditions (see Experimental Section) proceeded with moderate selectivity for substitution of Br to afford mainly the 5-amino-2-chloropyridine. More recently, we have described a method that offers improved selectivity for dihalopyridines of this type.[20,21]

The bicyclic diamines were prepared as outlined in Schemes 2 and 3. With the exception of **S-9** and **R-9**, these scaffolds were prepared and studied as racemates. The (1*S*,4*S*) enantiomer of *tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**S-9**) was commercially available, while the *N*-benzyl derivative of the (1*R*,4*R*) antipode **10** was available from *cis*-3-hydroxy-D-proline as described[22,23] and converted to Boc-protected diamine **R-9** using standard procedures. Likewise, racemic 2,5-diazabicyclo[2.2.2]octane **12** (Scheme 3) was accessible from 2,5-dibromoadipic acid according to the reported procedure.[24] In this case, heterocycle coupling (Pd method 'a') on the free diamine afforded the *N*-pyridinyl analogue **13**. Conversion of racemic benzyl 2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate to the ketone **14** was accomplished as described by Carroll et al.[25] Beckman rearrangement, and reduction of the resulting lactam, led to the Cbz-protected 2,6-diazabicyclo[3.2.1]octane **15**. Standard manipulation provided the diamine **18** with the opposite protecting group regiochemistry. These were, in turn, elaborated to the chloropyridines **17** and **20**, respectively.

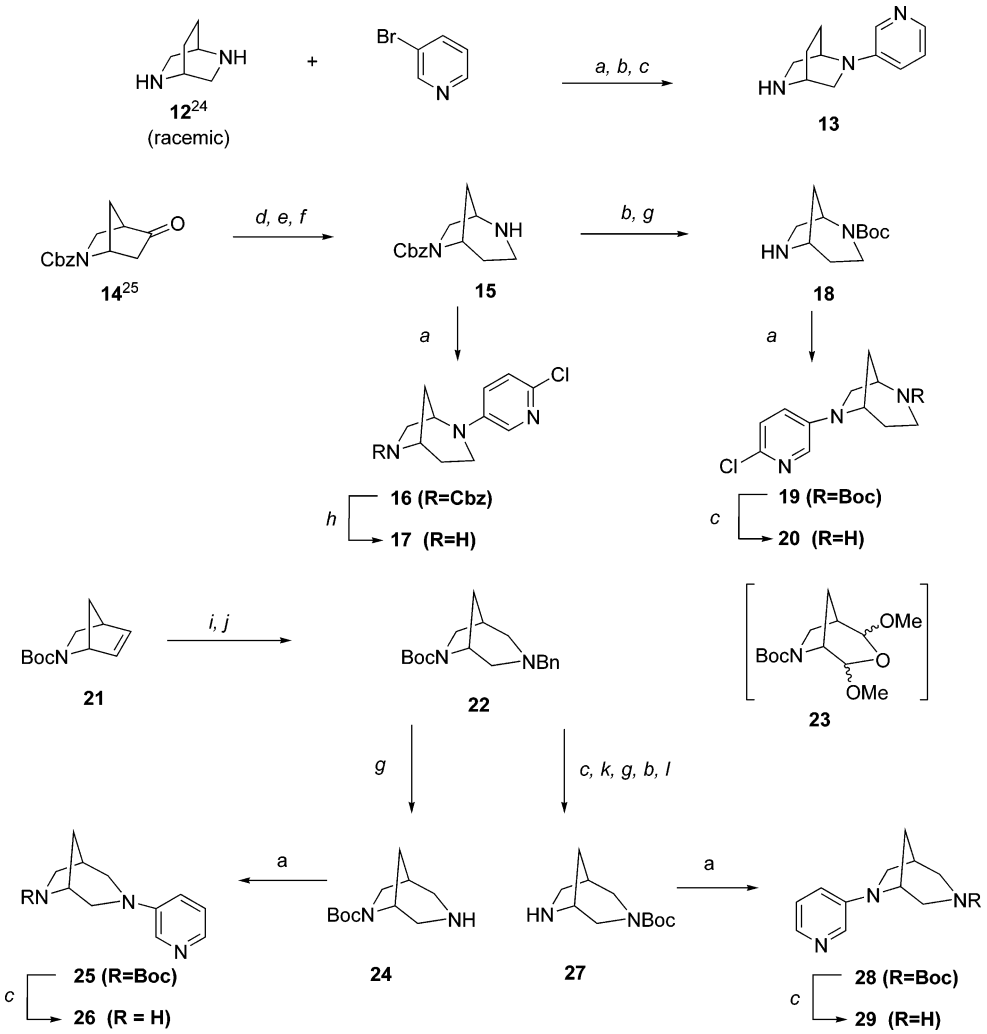
Ozonolysis of N-Boc-2-azanorbornene (**21**) in methanol and reductive amination with benzylamine by analogy to the reported method[26] provided the orthogonally protected 3,6-diazabicyclo-[3.2.1]octane **22**, but with very low (<20%) overall yield. The major byproduct (60%) was the acetal **23**, formed during ozonolysis in methanol and resistant to the reductive amination conditions. This problem was avoided by use of acetic acid in place of methanol as the carbonyl oxide trap during ozonolysis. The aldehyde derivatives produced under the modified conditions cycled efficiently through reductive amination, and the protected diamine **22** was formed in 77% isolated yield for the two-stage, one-pot process. Straightforward processing of protecting groups, around Pd-mediated coupling to the heterocycle, afforded either *N*-pyridinyl isomer of the diamine (**26**, **29**) with complete control of regiochemistry.

Biological Assays. Three different *in vitro* assays were employed to characterize the nAChR activity of these analogues. As a primary screen, all compounds were evaluated for their ability to displace [^{3}H]-cytisine from rat brain membranes according to the reported method.[27,28] Binding constants from this assay are taken to reflect affinities for the $\alpha4\beta2$ receptor. Nicotine exhibits nanomolar binding affinity in this assay, while epibatidine, one of the most potent nAChR ligands yet reported, is some 20-fold more potent with a binding constant (K_i) of 47 pM. The data in Table 1 indicates that several of the pyridinyldiamine analogues described here have binding potencies approaching or even exceeding that of epibatidine.

The high-affinity binding state of the nAChR is thought to involve a channel-closed, desensitized conformation of the receptor. Consequently, binding affinities measure interaction with that receptor state but reveal little about the ability of the ligand to activate the ion channel. To that end, functional activity at central NNR receptors was determined for selected compounds by measuring ligand-evoked release of dopamine from rat striatal slices.[29] The precise identity of receptors involved in this effect, once thought to involve predominately the $\alpha3\beta2$ subtype,[30] remains the subject of intense investigation. Recent studies incorporating detailed analysis of results from knockout mice have implicated several different receptor subtypes, including $\alpha6\beta3\beta2$, $\alpha4\alpha6\beta3\beta2$, $\alpha4\beta2$, and $\alpha4\alpha5\beta2$[31−34] as contributing to nAChR-mediated dopamine release. Interestingly, $\alpha3\beta2$ receptors do not seem to be involved in dopamine release from rodent striatum, although they may play a prominent role in primates.[35,36] In spite of the uncertainties regarding the precise contributions of these individual receptor types, activity in dopamine release is taken here as a measure of the ability of compounds to activate native nAChRs typical of those found in the CNS. Moreover, emerging data suggests that decreased dopamine levels in the striatum may be associated with pain states[37,38] and so enhanced dopamine release may contribute to the analgesic properties of nicotinic agonists. The *N*-pyridinyl diamines described herein are typically much more potent than nicotine (EC_{50} = 200 nM[29]) in this functional assay, with some exhibiting sub-nanomolar potencies comparable to that of epibatidine (EC_{50} = 0.83 nM).

Likewise, the ability of these compounds to activate ganglionic nAChRs was evaluated, since these receptors are thought to mediate some of the toxicities of nicotinic agonists.[10] For

Scheme 3. Syntheses of Bicyclic Diamines[a]



[a] (a) Pd_2dba_3, rac-BINAP, NaOtBu, halopyridine, toluene, 80 °C; (b) Boc_2O; (c) H^+; (d) NH_2OH; (e) TMSPP; (f) BH_3-SMe_2; (g) H_2, Pd−C or $Pd(OH)_2$-C; (h) TMSI; (i) O_3/CH_2Cl_2-HOAc; Me_2S; (j) $PhCH_2NH_2$, $NaBH_3CN$; (k) TFAA, Et_3N; (l) K_2CO_3, CH_3OH.

Table 1. Binding and Functional Activity of *N*-Pyridinyl-Bridged Bicyclic Diamines

	cytisine binding (α4β2)		IMR-32 FLIPR (α3β4*)		
compound	pK_i ((SEM)	K_i (nM)	pEC_{50} (±SEM)	EC_{50} (μM)	max. (%)
nicotine	9.03 ± 0.31	0.94	5.03 ± 0.31	9.44	94
epibatidine (**1**)	10.33 ± 0.13	0.047	7.56 ± 0.58	0.027	132
S-8	9.99 ± 0.20	0.10	6.35 ± 0.45	0.45	123
R-8	10.74 ± 0.10	0.018	6.84 ± 0.37	0.14	144
13	10.70 ± 0.23	0.020	6.56 ± 0.15	0.28	103
26	10.33 ± 0.23	0.047	7.15 ± 0.10	0.072	170
29	10.19 ± 0.01	0.065	5.80 ± 0.08	1.6	110
17	8.83 ± 0.07	1.5			
20	8.56 ± 0.07	2.8	5.13 ± 0.07	7.4	34
S-30	6.01 ± 0.25	980			
S-31	9.81 ± 0.18	0.15	5.19 ± 0.02	6.4	108
S-32	5.29 ± 0.04	5200			
S-33	8.89 ± 0.27	1.3			
S-34	7.47 ± 0.12	34			
S-35	9.69 ± 0.09	0.20	5.81 ± 0.27	1.5	22

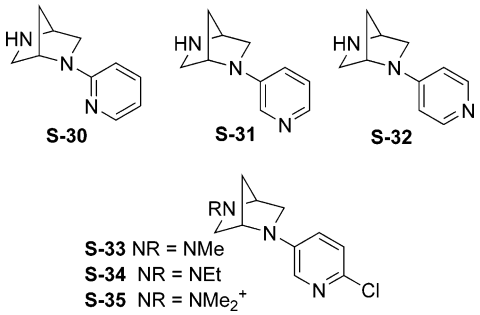
this assay, calcium influx to IMR-32 human neuroblastoma cells, which express ganglionic nAChRs (including the α3β4* subtype), was detected using FLIPR methodology according to the reported method.[39] This assay is taken to reflect activation of α3β4-containing nAChRs and by extension the potential for evoking gastrointestinal and cardiovascular side effects.

The tissue preparation of the dopamine release assay is quite different from the cultured cells used in the FLIPR experiment, so direct comparison of EC_{50}s across the assays is not appropriate. Instead, relative potencies within an assay are compared to a standard (e.g., epibatidine) to identify changes in selectivity for central vs ganglionic nAChR subtypes. Likewise, agonist efficacies (amount of DA release or Ca^{+2} influx) are normalized to the maximal effect of nicotine in that assay.

Results and Discussion

It is evident from the data in the Table 1 that these bicyclic diamines are effective scaffolds for construction of high-affinity

Scheme 4. Pyridine Regioisomers and N-Alkylation



nAChR ligands, including several with binding and functional potencies rivaling that of epibatidine. For example, the 6-chloropyridine derivatives of 2,5-diazabicyclo[2.2.1]heptane (entries **S-8** and **R-8**) have binding affinities at the α4β2 nAChR in the 20−100 pM range, comparable to that of epibatidine (**1**, 47 pM). One-carbon expansion of the alkylene bridge to a 2,5-diazabicyclo[2.2.2]octane (**13**) is accommodated with full retention of ligand potency. Insertion of a methylene group into the bridgehead-nitrogen bond likewise affords compounds (**26** and **29**) that retain exquisite affinity for the α4β2 binding site. On the other hand, while expansion of the aza-bridge in the opposite fashion (into the bridgehead-carbon bond, **17** and **20**) results in compounds with single-digit-nanomolar affinity, this represents an approximate 100-fold decrease in potency relative to the other bridged bicyclic diamines.

A similar trend pertains to the ability of these compounds to activate the ganglionic-type (α3β4*) nAChR as expressed in IMR-32 cells. In this assay, epibatidine is nearly 400-fold more potent than nicotine. Of the diamine derivatives, **26** displays potency and efficacy comparable to epibatidine. Interestingly, the regioisomer **29** is much less effective for activation of the α3β4* receptor subtype, even though it retains nearly equivalent binding affinity for the α4β2 nAChR. On the other hand, the much weaker binding affinity of the 2,6-diazabicyclo[3.2.1]-octanes (**17** and **20**) does translate to lower potency at the α3β4* receptor compared to the other diamine scaffolds.

Because of its high potency as well as the availability of individual enantiomeric forms, the 2,5-diazabicyclo[2.2.1]-heptane scaffold was chosen for more detailed evaluation of structure−activity relationships. Nicotinic affinity is strongly dependent on the position of attachment of the pyridine heterocycle (Scheme 4, **S-30**, **S-31**, **S-32**), with substitution at the 3-position (**S-31**) essential for good activity. The regioisomeric 2- and 4-pyridinyl motifs result in comparatively complete loss of ligand potency. A similar effect has been reported for epibatidine derivatives, where 2-and 4-pyridine substitution results in substantial decrement in functional activity at α4β2 and α3β4* receptors.[40]

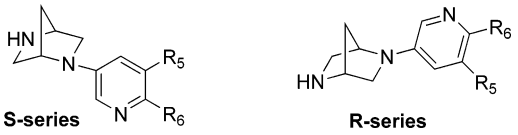
N-Methylation to the tertiary amine (**S-33**) causes an approximate 13-fold decrease in potency (compare **S-8**). The *N*-ethyl analogue (**S-34**) suffers a further 30-fold attenuation in binding potency. This contrasts with N-alkylation of (−)-epibatidine, where an *N*-methyl group is accommodated with little change in binding affinity[41] and even a modest increase in agonist activity.[42] N-Ethylation of epibatidine does, however, result in loss of binding affinity comparable to the cumulative effect on **S-34**.[41] In contrast, the *N*,*N*-dimethyl quaternary salt (**S-35**) exhibits binding affinity nearly at the level of the secondary amine, as observed previously in this series.[43] The functional activity, however, is not restored, as the quaternary salt **S-35** exhibits very weak partial agonist activity in IMR-32 cells.

Other critical structure−activity relationships concern the absolute stereochemistry of the diazanorbornane ring system (**S-8** vs **R-8**) as well as substitutions on the pyridine ring, which are known to influence functional potency and nAChR subtype selectivity for various ligand families.[44−46] Consequently, the effects of pyridine substitution on binding as well as functional activity were evaluated for both enantiomer series, and the data are listed in Table 2. Unlike (−)-epibatidine, which is nearly equipotent with its (+)-antipode,[42] ligand−receptor binding of 2,5-diazabicyclo[2.2.1]heptanes with nAChRs exhibits consistent enantioselectivity. In each case, the (*R*,*R*)-enantiomer exhibits higher binding affinity for the rat α4β2 receptor, with the eudismic ratio[47] ranging from ∼5-fold for 6-chloro and 5-methoxy analogues (**S-8**/**R-8** and **S-45**/**R-45**) to greater than 100-fold for the 5-hydroxypyridine derivatives (**S-43** and **R-43**). Functional activities in IMR-32 cells and dopamine release are also greater for the (*R*,*R*)-enantiomers, indicating that these different heteromeric nAChR subtypes (e.g., both α4- and α3-containing) share a similar preference for ligand stereochemistry.

Generally, modifications at the 2- and 4-positions of pyridinyl nAChR ligands are not well-tolerated, so these were not explored.[48,49] On the other hand, the 5-position accommodates a wide range of substitutions,[50,51] while only smaller groups are tolerated at the 6-position. These substitution patterns, therefore, were the focus of the present study. As noted for other nicotinic compounds,[52,53] halogen at the pyridine 6-position maintains or even enhances potency; in this case chlorine and fluorine are similarly effective (**S-8, R-8**, **S-36**, **R-36**). The 6-methyl (**S-37**) and 6-methoxy (**R-38**) groups result in modest (10-fold) loss of binding affinity compared with the respective H-substituted analogues. Finally, both the electron-donating 6-amino (**S-40**) and the electron-withdrawing 6-nitro (**S-39**) groups cause more dramatic (100 and 500-fold, respectively) attenuation of binding potency, similar effects to the equivalent substitutions on nicotine.[53]

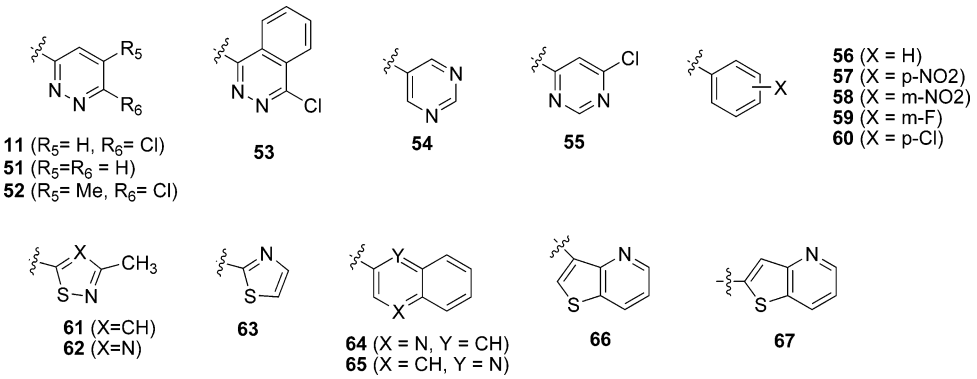
A 5-methyl substitution (**R-46**) retains excellent affinity for the α4β2 receptor, but the trifluoromethyl group is clearly detrimental (**R-47**). Likewise, aminomethyl substitution is not favorable (**S-42**), but cyano (**S-41** and **R-41**) is reasonably well-tolerated. In general, binding affinities of the (*S*,*S*)-enantiomer series appear to be more sensitive to substitution, and certain groups result in very pronounced enantiomer differentiation at nAChRs. The (*R*,*R*)-enantiomer of the 5-carboxamide (**R-50**) binds to the α4β2 receptor with 30-fold higher affinity than the (*S*,*S*)-isomer (**S-50**). Even more dramatic is the 100-fold difference in binding potency for the 5-hydroxyl analogues (**S-43** vs **R-43**). This is also manifested in functional activity in IMR-32 cells, since the (*R*,*R*) enantiomer (**R-43**) activates the α3β4* nAChR with micromolar potency and high efficacy, while **S-43** does not induce significant ion flux even at 100 μM. On the other hand, both **R-43** and **S-43** exhibit relatively potent activity in the dopamine release assay, indicating that these substituents modulate functional activity differently for the respective nAChR subtypes. Indeed, **S-43** is 7-fold more potent than nicotine toward activation of central nAChRs involved in dopamine release but more than 10-fold weaker at ganglionic nAChRs, implying an overall 70-fold increase in subtype selectivity for **S-43** relative to nicotine. In particular, hydrophilic substituents at the pyridine 5-position seem to attenuate the activity at IMR-32 cells, while maintaining potency for dopamine release, and offer the potential for developing more selective agonists. Among these, the 5-hydroxy (**S-43**, **S-44**, and **R-44**) and 5-carboxamide (**S-50** and **R-50**) substituents provide the best improvement in functional selectivity.

Table 2. Pyridine Substituent Effects on nAChR Activity



			cytisine binding (α4β2)		IMR-32 FLIPR (α3β4*)			striatal dopamine release		
compound	R_5	R_6	pK_i (± SEM)	K_i (nM)	pEC$_{50}$	EC$_{50}$ (μM)	max (%)	pEC$_{50}$ (± SEM)	EC$_{50}$ (nM)	max. (%)
nicotine	-	-	9.03 ± 0.31	0.94	5.03 ± 0.31	9.4	94	6.70 ± 0.20	200	100
1	-	-	10.33 ± 0.13	0.047	7.56 ± 0.58	0.027	132	9.08 ± 0.08	0.83	88
S-31	H	H	9.81 ± 0.18	0.15	5.19 ± 0.02	6.4	108	6.86 ± 0.29	138	117
R-31	H	H	10.74 ± 0.11	0.018	6.43 ± 0.21	0.37	64			
S-8	H	Cl	9.99 ± 0.20	0.10	6.35 ± 0.45	0.45	123	8.28 ± 0.12	5.3	114
R-8	H	Cl	10.74 ± 0.10	0.018	6.84 ± 0.37	0.14	144	8.60 ± 0.23	2.5	121
S-36	H	F	9.85 ± 0.09	0.17	5.43 ± 0.16	3.7	133	7.72 ± 0.23	19	167
R-36	H	F	10.55 ± 0.10	0.028	6.79 ± 0.13	0.16	94	8.79 ± 0.23	1.6	153
S-37	H	CH_3	8.80 ± 0.09	1.6	5.76 ± 0.28	1.7	98	6.46 ± 0.23	350	137
R-38	H	OCH_3	9.60 ± 0.05	0.25	6.07 ± 0.04	0.85	97			
S-39	H	NO_2	6.96 ± 0.19	110	4.95 ± 0.09	11	62			
S-40	H	NH_2	7.70 ± 0.19	20	4.51 ± 0.26	31	79			
S-41	CN	H	8.79 ± 0.06	1.7	4.61 ± 0.27	24	24	7.64 ± 0.26	23	104
R-41	CN	H	10.57 ± 0.21	0.027	6.01 ± 0.06	0.98	92	9.10 ± 0.15	0.80	148
S-42	CH_2NH_2	H	6.85 ± 0.13	140	4.70 ± 0.51	20	10			
S-43	OH	H	8.39 ± 0.24	4.0	< 4	>100	19	7.60 ± 0.09	28	131
R-43	OH	H	10.45 ± 0.13	0.035	5.58 ± 0.01	2.6	149	8.24 ± 0.35	5.7	148
S-44	OH	Cl	8.80 ± 0.27	1.6	4.46 ± 0.16	35	90	7.30 ± 0.42	51	120
R-44	OH	Cl	9.76 ± 0.06	0.17	5.49 ± 0.02	3.2	121	8.42 ± 0.24	3.8	128
S-45	OCH_3	H	9.28 ± 0.24	0.53	4.52 ± 0.12	30	39	7.09 ± 0.90	81	122
R-45	OCH_3	H	9.90 ± 0.12	0.12	5.24 ± 0.12	5.7	86	7.70 ± 0.06	20	117
R-46	CH_3	Cl	10.87 ± 0.14	0.014	6.74 ± 0.13	0.18	87			
R-47	CF_3	H	6.31 ± 0.34	490		nd				
R-48	Cl	Cl	10.74 ± 0.12	0.018	6.26 ± 0.32	0.55	83	7.79 ± 0.86	16	144
R-49	OCH_3	Cl	10.00 ± 0.26	0.10	5.37 ± 0.21	4.3	69			
S-50	$CONH_2$	H	7.62 ± 0.11	24	4.59 ± 0.01	25	12			
R-50	$CONH_2$	H	9.08 ± 0.18	0.83	4.55 ± 0.05	28	58	7.52 ± 0.92	30	97

Scheme 5. Pyridine Replacements



While pyridine appears to be the optimal heterocycle for these nAChR ligands, other heteroaryl systems are also effective (Table 3, Scheme 5). Since structure−affinity effects on binding potencies are more pronounced in the (*S*,*S*)-enantiomer series, this survey of pyridine replacements focused mainly on derivatives of **S-9**. Pharmacophore models suggest that the pyridine nitrogen functions as a hydrogen bond acceptor[54] and only heterocycles bearing a suitably placed surrogate exhibit potency as nAChR ligands. Pyridazines linked at the 3-position possess this critical nitrogen and retain binding potencies in the nanomolar range, albeit significantly weaker than the corresponding pyridines. Typically, 6-chloro substitution enhances pyridazine potency, and that is the case here (**S-11**[43] vs **S-51**). As for the pyridines, the heteroaryl (*R*,*R*)-diamine (**R-11**) is the more potent enantiomer. A 5-methyl group is well-tolerated (**S-52**), as it is on pyridine (*vide supra*), but ring fusion across the 4,5-position (**S-53**) is not. The 5-pyrimidinyl analogue **S-54** can be viewed as a hybrid of opposite 3-pyridinyl rotamers about the diamine−heterocycle bond, and subnanomolar binding affinity is maintained in this compound. As expected, the 4-pyrimidinyl analogue **S-55**, representing superposition of the 2-and 4-pyridinyl motifs, is significantly less potent. Phenyl derivatives (**S-56** to **S-60**), lacking the ring nitrogen altogether, are poor substitutes for pyridine. Nevertheless, it is interesting to note that the potency of these analogues is enhanced by substitution, as previously described for the corresponding aryl ethers.[55] In contrast to the aryl ethers where meta-substitution seems best, the more potent phenyldiamine ligands result from para-substitution.

The presence of an *o*-aza moiety in the heterocycle is detrimental to binding affinity. This may contribute to the lower activity of pyridazines compared to pyridines as noted above, but is also evident with other heterocycles. Thus, the 3-methylisothiazol-5-yl derivative **S-61** exhibits nanomolar potency at the α4β2 nAChR, but the analogous thiadiazole **R-62**, as well as the 2-thiazole **S-63**, is comparatively inactive.

Table 3. Evaluation of Pyridine Replacements on the 2,5-Diazabicyclo[2.2.1]heptane Scaffold

configuration and aryl group	cytisine binding (α4β2) pK_i (± SEM)	K_i (nM)
S-11	8.05 ± 0.06	8.8
R-11	9.61 ± 0.06	0.24
S-51	6.91 ± 0.12	120
S-52	8.42 ± 0.26	3.8
S-53	5.72 ± 0.26	1900
S-54	9.02 ± 0.14	0.95
S-55	7.28 ± 0.15	52
S-56	6.00 ± 0.05	1000
S-57	7.17 ± 0.19	67
S-58	6.22 ± 0.13	600
S-59	6.60 ± 0.17	250
S-60	7.65 ± 0.09	22
S-61	8.31 ± 0.10	4.9
R-62	6.45 ± 0.10	350
S-63	5.63 ± 0.22	2300
S-64	7.77 ± 0.12	17
S-65	5.40 ± 0.03	4000
R-66	6.55 ± 0.20	280
R-67	9.08 ± 0.24	0.83

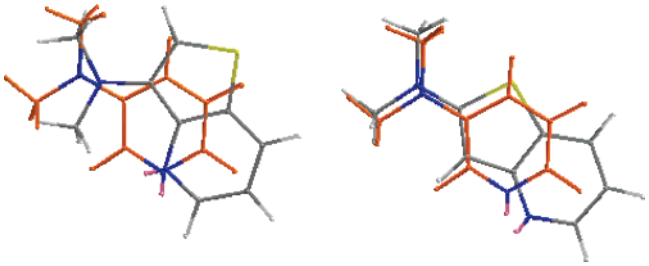
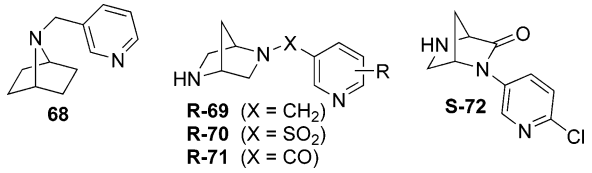


Figure 1. Overlay of 3-pyridinylamine (orange shading) with (left) 3-thieno[3,2-*b*]pyridinylamine (**66**) and (right) 2-thieno[3,2-*b*]pyridinylamine (**67**), illustrating better alignment of pharmacophore elements in the latter (structures generated with Chem3D software).

Table 4. Alternative Linkers from Heterocycle to Amine

compound	R	cytisine binding (α4β2) pK_i (± SEM)	K_i (nM)
R-69	H	7.25 ± 0.30	56
R-70	5-Br, 6-Cl	7.77 ± 0.26	17
R-71	6-Cl	6.23 ± 0.34	590
S-72	6-Cl	>4	>10000

Scheme 6. Alternative Pyridine Attachments



Fused bicyclic heteroaromatics have also been investigated. The 3-quinolinyl derivative **S-64**, corresponding to benzene fusion across the 5,6-position of pyridine, retains modest activity, but the 2-quinolinyl regiosiomer **S-65** does not. Interestingly, the 2-substituted thieno[3,2-b]pyridine **R-67** is a good replacement for pyridine, but the 3-substituted isomer **R-66** is not. Superposition of each of these heterocycles with 3-pyridinyl (Figure 1) reveals that the former presents a closer alignment of the pyridine lone pairs. Moreover, attempts to align those elements with the 3-substituted thieno[3,2-b]pyridine projects the fused ring into the space around the pyridine-4-position, where substitution is typically disfavored.[48]

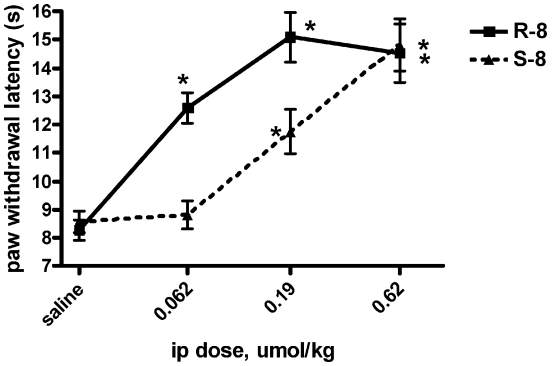


Figure 2. Antinociceptive effects of **S-8** and **R-8** evidenced by increased latency to withdrawal from a noxious thermal stimulus (rat hot box).

Trudell and co-workers[56] have disclosed the pyridinylmethyl analogue of epibatidine (**68**) (Scheme 6) as a moderately potent nAChR ligand (K_i = 98 nM). That derivative of the (*R*,*R*)-2,5-diazabicyclo[2.2.1]heptane scaffold (**R-69**) has similar activity (Table 4), though it should be noted that this represents a 3000-fold loss of binding affinity relative to the pyridinylamine **R-31**. Other spacers were also evaluated. The sulfonamide **R-70** exhibits potency comparable to **R-69**, but the nicotinamide **R-71** is much less active. A different amide construct, in the lactam **S-72**, is likewise not well tolerated.

Analgesic Activity. Consistent with their high affinity and potent activity at centrally disposed nAChR subtypes, these compounds exhibit analgesic properties across a range of rodent pain models. Since the presence of a 6-chloro substituent on the pyridine ring appears to enhance analgesic activity of a number of nicotinic agonists (including nicotine,[57] epibatidine,[58] and **3**[52]), these analogues were selected for initial evaluation. Thus, **S-8** produced a dose-dependent increase in withdrawal latency in response to acute noxious thermal pain, as measured in the rat hot box (Figure 2). The analgesic effect was completely blocked by pretreatment with the nicotinic antagonist mecamylamine (see Supporting Information). The greater *in vitro* potency of the (*R*,*R*)-enantiomer **R-8** translates to a leftward shift of the analgesic dose response curve relative to (*S*,*S*) **S-8**.

Analgesics do not affect all pain states equally. Different types of pain can involve different signaling mechanisms,[59,60] and a drug that is effective for one pain condition may not work well for another. An attractive feature of nAChR agonists is that they appear to have broad-spectrum efficacy in a variety of pain models.[61] In addition to the acute thermal nociception measured in the rat hot box, **S-8** was effective in reducing the number of flinches in the phase II response to subcutaneous injection of formalin solution into the rat hindpaw (Figure 3), a model for a persistent pain involving central and peripheral sensitization that is considered to have clinical relevance.[62,63] Likewise, **S-8** reversed the mechanically stimulated hyperalgesia following spinal nerve ligation in rat (the Chung model of neuropathic pain).[64]

Across these models, the analgesic effects of **S-8** were observed at doses ranging from 0.19−6.2 μmol/kg ip. Unfortunately, behavioral side effects (hypolocomotion, increased urination, head weaving) were evident at higher doses, and a dose of 62 μmol/kg ip caused seizures in mice (data not shown). These results define a relatively narrow therapeutic window for **S-8** and indicate that this compound is not a good candidate for clinical development. As noted above, improved nAChR subtype selectivity vs **S-8** was achieved with hydrophilic substituents in the pyridine 5-position (e.g., **R-44**, Table 2).

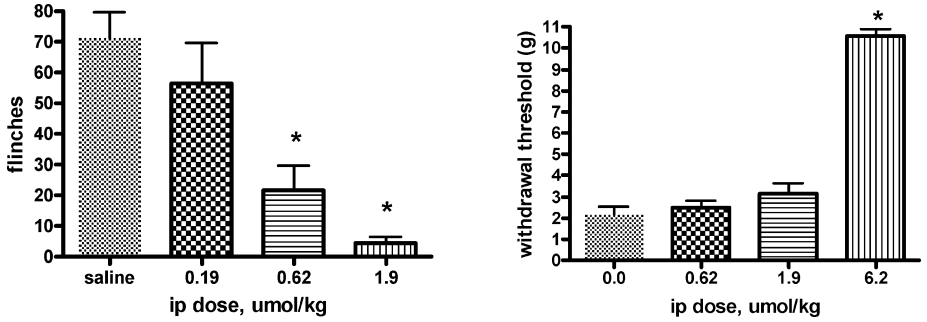


Figure 3. Analgesic efficacy of **S-8** in the rat formalin model of persistent pain (left panel) and in the spinal nerve ligation model of neuropathic pain (right panel).

While **R-44** has similar activity to **S-8** in the dopamine release assay, it is nearly 9-fold less potent at the ganglionic nAChR subtype. The *in vivo* results, however, were disappointing, as **R-44** was only partially efficacious in the rat formalin assay at doses up to 6.2 μmol/kg ip, and doses as high as 19 μmol/kg ip failed to reverse allodynia in the rat Chung model (data not shown). It is likely that this failure is due to inefficient partitioning of **R-44** into the CNS. Although anti-allodynic effects of nAChR agonists are known to be mediated by both central and peripheral receptors, it has been suggested that agonists achieving simultaneous activation of both populations will produce effects at substantially lower doses than those acting at either site alone.[65]

In the case of **R-44**, the 5-hydroxyl substituent that confers improved subtype selectivity also inhibits distribution of this compound into the CNS. Although **R-44** was rapidly absorbed following ip dosing, achieving maximal plasma levels in rat within 15 min of administration, little of this drug reached the brain. Brain levels of **R-44** also peak by the 15 min time point and began to fall as plasma levels cleared within 1 h. During this time frame, which is relevant to the analgesia assays, the brain concentration of **R-44** averaged only 6−8% of that in plasma (see Supporting Information). Consequently, gains in receptor selectivity with **R-44** were undercut by its low level of CNS penetration. Presumably, with its action limited mainly to peripheral sites, achieving *in vivo* efficacy with **R-44** would require higher doses than those tested here. Similar results pertain to other selective compounds in Table 2. To date, we have been unable to identify substitution patterns in this series that led to suitable *in vitro* selectivity without also compromising the CNS access. Nevertheless, the SAR trends indicate that functional selectivity is achievable, if substitutions more compatible with CNS penetration can be identified.

Conclusions

Bridged bicyclic diamines are useful scaffolds for construction of exceptionally potent ligands for nicotinic acetylcholine receptors, some rivaling the affinity of epibatidine for the $\alpha4\beta2$ subtype. Many of the compounds are agonists at central and ganglionic receptors, but pyridine substituents, particularly in the 5-position, appear to differentially modulate the activities at those subtypes, suggesting modifications that can enhance receptor selectivity. Compounds from the series exhibit broad spectrum analgesic properties across rodent models for acute thermal nociception, persistent pain, and neuropathic pain. Unfortunately, the hydrophilic pyridine substituents that favor selective activation of central vs ganglionic nAChRs also tend to limit distribution of the compounds into the CNS, a critical factor in achieving analgesic efficacy for this class of compounds.

Experimental Section

General. Unless otherwise specified, all reagents and solvents were obtained from commercial suppliers and were used without further purification. Flash chromatography was performed using silica gel (230−400 mesh) from EM Science, or prepacked columns supplied by Analogix. Proton NMR spectra were recorded at 300 MHz in the solvent indicated, and chemical shifts are listed in ppm downfield of internal tetramethylsilane. Mass spectra were obtained in chemical ionization mode (DCI/NH_3), and only parent ions are listed. Elemental analyses were performed by Robertson Microlit Laboratories (Madison, NJ) or QTI Inc (Whitehouse, NJ).

Preparation of Heteroaryl Halides. 5-Bromo-3-pyridinol. 3-(Benzyloxy)-5-bromopyridine[66] (15.0 g, 56.8 mmol) and 30% HBr/HOAc (200 mL) were stirred at room temperature for 16 h. The reaction mixture was diluted with diethyl ether (500 mL), and the resulting white solid (12.9 g) was isolated by filtration. The solid was taken up in methanol (300 mL), and concentrated NH_4-OH (50 mL) was added. The resulting solution was stirred at room temperature for 12 h and then concentrated under reduced pressure to provide the title compound (9.8 g, 89%) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.42 (dd, J = 3, 2 Hz, 1H), 8.06 (d, J = 3 Hz, 1H), 8.10 ppm (d, J = 2 Hz, 1H); MS (DCI/NH_3) m/z 174, 176 $(M + H)^+$.

5-Bromo-2-chloro-3-pyridinol. A solution of 5-bromo-3-pyridinol (9.8 g, 56.3 mmol) in water (100 mL) and NaOH (2.40 g, 100 mmol) was treated with NaOCl (35 mL of 10% solution). The reaction mixture was stirred at ambient temperature for 16 h, quenched with acetic acid (5 mL), and extracted with ethyl acetate (500 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (3% CH_3OH in CH_2Cl_2) to provide the title compound (11.20 g, 96% yield) as a yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.45 (d, J = 2 Hz, 1H), 7.94 ppm (d, J = 2 Hz, 1H); MS (DCI/NH_3) m/z 208, 210 $(M + H)^+$.

5-Bromo-2-chloro-3-(methoxymethoxy)pyridine. A solution of 5-bromo-2-chloro-3-pyridinol (11.2 g, 53.1 mmol) in diethyl ether (50 mL) was added to a suspension of NaH (1.69 g, 70 mmol) in DMF (300 mL) and diethyl ether (60 mL). The mixture was stirred at room temperature for 30 min, and then a solution of chloromethyl methyl ether (5.65 g, 70 mmol, Aldrich Chemical Co.) in diethyl ether (30 mL) was added. The mixture was stirred at room temperature for 2 h and then quenched by cautious addition of water (200 mL). The aqueous mixture was extracted with diethyl ether (300 mL), and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (hexanes−EtOAc, 80:20) to provide the title compound (8.29 g, 61% yield) as a colorless oil, suitable for amine coupling reactions: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 3H), 5.27 (s, 2H), 7.64 (d, J = 2 Hz, 1H), 8.12 ppm (d, J = 2 Hz, 1H); MS (DCI/NH_3) m/z 252, 254 $(M + H)^+$.

5-Bromo-2-chloro-3-methoxypyridine. A solution of 5-bromo-2-chloro-3-pyridinol (1.2 g, 5.8 mmol) in diethyl ether (5 mL) was added to a suspension of NaH (181 mg, 7.5 mmol) in dry DMF (30 mL) and diethyl ether (6 mL). The mixture was stirred at room temperature for 30 min, and a solution of iodomethane (1.06 g,

7.5 mmol) in diethyl ether (3 mL) was added. The reaction was stirred 30 min longer, quenched with water (20 mL), and extracted with diethyl ether (100 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by column chromatography (hexanes−ethyl acetate, 80:20) to provide the title compound (0.32 g, 25%) as a colorless oil. MS(DCI/NH_3) *m/z* 222/224/226 $(M + H)^+$.

3-Bromo-5-cyanopyridine. A mixture of 5-bromo-nicotinamide (44.7 g, 222 mmol, Aldrich) and $POCl_3$ (110 mL) was heated in an oil bath to gentle reflux (120 °C) with stirring for 100 min. The solution was cooled to <30 °C and concentrated under vacuum to remove most of the excess $POCl_3$. The thick residue was diluted with dichloromethane ((300 mL) and poured onto ice (500 g). Solid K_2CO_3 (100 g) was added to bring the quench mixture to pH > 7. The organic layer was separated and concentrated under vacuum. The residue was returned to the aqueous quench mixture, which was extracted with ethyl acetate (2 × 500 mL). The combined extract was washed successively with 20% K_2CO_3 (aq, 100 mL) and saturated brine (100 mL), dried ($MgSO_4$), and concentrated to leave the title compound as an off-white solid (39.1 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (t, J = 1.9 Hz, 1H), 8.82 (br s, 1H), 8.90 ppm (br s, 1H).

5-Fluoro-2-nitropyridine. Aqueous hydrogen peroxide (9M, 20 mL) was added slowly and cautiously to well-cooled (dry ice-acetone) fuming sulfuric acid (50 mL) so that the internal temperature remains below 0 °C. A solution of 2-amino-5-fluoropyridine (4.00 g, 35.7 mmol) in sulfuric acid (8 mL) was added dropwise over 15 min, and the dark mixture was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for 1 h longer. The mixture was poured onto ice (200 g) and quenched with saturated sodium thiosulfate (negative starch−iodide test) and partially neutralized with solid Na_2CO_3. The mixture was extracted with EtOAc (3 × 100 mL), and the combined extract was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (hexanes−EtOAc 95:5 to 20:80) to provide the title compound as an oil that partially crystallizes (2.1 g, 41%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.80 (m, 1H), 8.35 (dd, J = 9, 4 Hz, 1H), 8.49 ppm (d, J = 3 Hz, 1H).

5-Bromo-2-chloropyridine. A 3 L three-necked round-bottom flask with mechanical stirrer was charged with 5-amino-2-chloropyridine (50.0 g, 389 mmol). Aqueous HBr (48%, 120 mL) was added, and the mixture was stirred vigorously with ice cooling to bring the internal temperature <5 °C. A solution of $NaNO_2$ (29.0 g, 420 mmol) in water (100 mL) was added dropwise over 15 min (mild exotherm, gas evolution, temperature maintained <5 °C) and the mixture was stirred for 5 min longer at 0−5 °C. Solid CuBr (29.0 g, 202 mmol) was added in small portions over 15 min with addition of water (200 mL total) as needed to maintain a fluid reaction mixture. Finally, the reaction mixture was diluted with more water (400 mL), and a simple distillation head was fitted to the reaction flask. The aqueous mixture was distilled until the distillate ran clear (~600 mL). The distillate was extracted with EtOAc (1 × 400 mL, 1 × 300 mL), and the combined extract was washed with brine (150 mL), dried ($MgSO_4$), and concentrated under vacuum to provide the title compound as a white solid (51.1 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 9 Hz, 1H), 7.77 (dd, J = 9, 3 Hz, 1H), 8.46 ppm (d, J = 3 Hz, 1H); MS (DCI/NH_3) *m/z* 192/194/196 $(M + H)^+$.

***tert*-Butyl (1*S*,4*S*)-5-(6-Nitro-3-pyridinyl)-2,5-diazabicyclo-[2.2.1]heptane-2-carboxylate (Boc-S-39): General Method 'b' for Thermal Amination of Heterocycles.** Triethylamine (0.5 mL, 3.6 mmol) was added to a solution of *tert*-butyl (*S*,*S*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**S-9**, 99 mg, 0.50 mmol) and 5-fluoro-2-nitropyridine (96 mg, 0.67 mmol) in toluene (5 mL). The solution was heated at 100 °C for 28 h, cooled to room temperature and concentrated under vacuum. The residue was purified by flash chromatography (eluting with hexanes−EtOAc, 70:30 to 20:80) to provide the title compound as a bright yellow solid (71 mg, 44%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32−1.51 (two br s., 9H), 1.91−2.14 (m, 2H), 3.23−3.72 (m, 4H), 4.46−4.82 (m, 2H), 6.89 (dd, J = 9, 3 Hz, 1H), 7.84 (br. s, 1H), 8.18 ppm (d, J = 9 Hz, 1H).

(1*S*,4*S*)-2-(6-Nitro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluenesulfonate (S-39). *tert*-Butyl (1*S*,4*S*)-5-(6-nitro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (Boc-**S-39**, 70 mg, 0.22 mmol) was dissolved in hot EtOAc (5 mL), and a solution of *p*-toluenesulfonic acid monohydrate (48 mg, 0.25 mmol) in EtOAc (3 mL) was added. The mixture was heated at reflux for 3 h, and ethanol (5 mL) was added with heating to dissolve the precipitate. The solution was cooled to −20 °C and filtered to provide the title salt as a tan, crystalline solid (71 mg, 84%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.13 (d, J = 12 Hz, 1H), 2.33 (d, J = 12 Hz, 1H), 2.33−2.41 (m, 3H), 3.32−3.48 (m, 2H), 3.52 (dd, J = 11, 2 Hz, 1H), 3.83 (dd, J = 11, 2 Hz, 1H), 4.59 (s, 1H), 4.95 (s, 1H), 7.22 (d, J = 8 Hz, 2H), 7.24−7.35 (dd, J = 9, 3 Hz, 1H), 7.70 (d, J = 8 Hz, 2H), 7.94 (d, J = 3 Hz, 1H), 8.23 ppm (d, J = 9 Hz, 1H). Anal. ($C_{10}H_{12}N_4O_2 \cdot C_7H_8SO_3$) C, H, N.

***tert*-Butyl (1*S*,4*S*)-5-(6-Chloro-3-pyridinyl)-2,5-diazabicyclo-[2.2.1]heptane-5-carboxylate (Boc-S-8): General Method 'a' for Pd-Mediated Coupling of Heterocycles.** A solution of racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, 75 mg, 0.12 mmol) and tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3, 56 mg, 0.06 mmol) in toluene (30 mL) was stirred under N_2 at 90 °C for 10 min and cooled to 40 °C. *tert*-Butyl (1*S*,4*S*)-2,5-diazabicyclo-[2.2.1]heptane-2-carboxylate (**S-9**, 600 mg, 3.03 mmol), 5-bromo-2-chloropyridine (641 mg, 3.33 mmol), and sodium *tert*-butoxide (465 mg, 4.84 mmol) were added, and the mixture was stirred at 80−85 °C under N_2 for 5 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and filtered through diatomaceous earth. The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel (hexanes−EtOAc, 3:1 to 1:1).

***tert*-Butyl (1*S*,4*S*)-5-(5-bromopyridin-2-yl)-2,5-diazabicyclo-[2.2.1]heptane-2-carboxylate** was the first-eluting component and obtained as a yellow solid (110 mg, 10% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 and 1.47 (s, 9H, Boc rotamers), 1.94 (m, 2H), 3.28−3.53 (m, 4H), 4.51 and 4.66 (br s, 1H), 4.75 and 4.85 (br s, 1H), 6.24 (d, J = 9 Hz, 1H), 7.50 (dd, J = 9, 2 Hz, 1H), 8.13 ppm (d, J = 2 Hz, 1H); MS (DCI/NH_3) *m/z* 354/356 $(M + H)^+$. This material was used for the preparation of **S-30**.

***tert*-Butyl (1*S*,4*S*)-5-(6-chloropyridin-3-yl)-2,5-diazabicyclo-[2.2.1]heptane-2-carboxylate (Boc-S-8)** was the second-eluting material, also obtained as a yellow solid (540 mg, 58% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 and 1.47 (s, 9H, Boc rotomers), 1.98 (m, 2H), 3.15 (m, 1H), 3.40 (m, 2H), 3.57 (br d, J = 10 Hz, 1H), 4.37 (br s, 1H), 4.52 and 4.65 (br s, 1H), 6.68 (dd, J = 9, 3 Hz, 1H), 7.12 (br d, J = 9 Hz, 1H), 7.70 ppm (br s, 1H); MS (DCI/NH_3) *m/z* 310/312 $(M + H)^+$.

(1*S*,4*S*)-2-(6-Chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluenesulfonate (S-8). A solution of *p*-toluenesulfonic acid monohydrate (190 mg, 1.0 mmol) in warm ethyl acetate (10 mL) was added to a boiling solution of Boc-**S-8** (309 mg, 1.0 mmol) in ethyl acetate (40 mL) and ethanol (10 mL). The solution was stirred at reflux for 20 h and then cooled to room temperature. The precipitated solid was isolated by filtration, washed with ethyl acetate, and dried under vacuum to provide the title salt as a white powder (253 mg, 68% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 2.06 (br d, J = 11 Hz, 1H), 2.29 (br d, J = 11 Hz, 1H), 2.36 (s, 3H), 3.32 (m, 1H), 3.35 (s, 2H), 3.74 (dd, J = 11, 2 Hz, 1H), 4.52 (br t, J = 2 Hz, 1H), 4.71 (br s, 1H), 7.16 (dd, J = 9, 3 Hz, 1H), 7.22 (d, J = 8 Hz, 2H), 7.27 (d, J = 9 Hz, 1H), 7.69, (d, J = 8 Hz, 2H), 7.78 ppm (d, J = 3 Hz, 1 H); MS (DCI/NH_3) *m/z* 210/212 (M + H)$^+$; Anal. ($C_{10}H_{12}N_3Cl \cdot C_7H_8SO_3$) C, H, N.

(1*S*,4*S*)-2-(6-Chloro-3-pyridinyl)-5-methyl-2,5-diazabicyclo-[2.2.1]heptane *p*-Toluenesulfonate (S-33). Aqueous formalin (37%, 1 mL) was added to a solution of Boc-**S-8** (106 mg, 0.34 mmol) in formic acid (3 mL), and the mixture was heated to 100 °C for 1 h. The solution was cooled to room temperature and concentrated under vacuum, and the white solid residue was purified by flash chromatography on silica gel (CH_2Cl_2−CH_3OH−$^cNH_4$-OH, 90:10:1) to provide the free base of **S-33**. The free base was

taken up in ethyl acetate (5 mL), filtered to remove some paraformaldehyde, and the filtrate was added to a solution of *p*-toluenesulfonic acid monohydrate (65 mg, 0.34 mmol) in ethyl acetate (5 mL). The mixture was warmed to reflux with addition of 5 drops of ethanol to dissolve the solids. On cooling, the salt crystallized to provide 106 mg (78%) of the title salt as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.30 (br d, $J = 11$ Hz, 1H), 2.36 (s, 3H), 2.39 (br d, $J = 11$ Hz, 1H), 2.96 (s, 3H), 3.30 (m, 1H, obscured by solvent), 3.41 (m, 1H), 3.65 (m, 1H), 3.75 (dd, $J = 11$, 3 Hz, 1H), 4.41 (br s, 1H), 4.71 (br s, 1H), 7.16 (dd, $J = 9$, 3 Hz, 1H), 7.23 (d, $J = 8$ Hz, 2H), 7.28 (d, $J = 9$ Hz, 1H), 7.69, (d, $J = 8$ Hz, 2H), 7.78 ppm (d, $J = 3$ Hz, 1H); MS (DCI/NH_3) *m*/*z* 224/226 $(M + H)^+$; Anal. ($C_{11}H_{14}N_3Cl \cdot C_7H_8SO_3 \cdot 0.25\ H_2O$) C, H, N.

(1*S*,4*S*)-2-(6-Chloro-3-pyridinyl)-5,5-dimethyl-2,5-diazabicyclo-[2.2.1]heptanium Iodide (S-35). Methyl iodide (1.0 g, 7 mmol) was added to a stirred solution of the free base of **S-33** (91 mg, 0.40 mmol) in ether (15 mL). After 19 h, the precipitate was collected by filtration, washed thoroughly with ether, and dried under vacuum at 50 °C to provide **S-35** as an off-white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.46 (m, 1H), 2.71 (br d, $J = 12$ Hz, 1H), 3.11 (s, 3H), 3.32 (s, 3H), 3.70 (m, 3H), 3.92 (br d, $J = 13$ Hz, 1H), 4.57 (br s, 1H), 4.73 (br s, 1H), 7.18 (dd, $J = 9$, 3 Hz, 1H), 7.29 (d, $J = 9$ Hz, 1H), 7.81 ppm (d, $J = 3$ Hz, 1H); Anal. ($C_{12}H_{17}N_3Cl \cdot I$) C, H, N.

(1*S*,4*S*)-2-(6-Chloro-3-pyridinyl)-5-ethyl-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluenesulfonate (S-34). A solution of **S-8** (free base, 60 mg, 0.29 mmol) in dichloromethane (4 mL) was stirred with ice-cooling as acetaldehyde (300 μL, 5 mmol) and $NaBH(OAc)_3$ (163 mg, 0.77 mmol) were added. The mixture was allowed to warm slowly to room temperature (2 h) and then concentrated under vacuum. The residue was purified by chromatography (silica gel, $CH_2Cl_2-CH_3OH-{}^cNH_4OH$ 90:10:1) to provide the N-ethylated free base **S-34** (20 mg, 29% yield). This was taken up in EtOAc (3 mL) and treated with a solution of *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol) in warm EtOAc (4 mL). The resulting precipitate was dissolved by addition of ethanol (1 mL) and warming and the solution allowed to cool. The resulting crystals were isolated by filtration and dried under vacuum to provide the title salt (27 mg, 23% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 1.32 (t, $J = 7$ Hz, 3 H), 2.34 (m, 2H), 2.36 (s, 3H), 3.22 (m, 2H), 3.40 (m, 2H), 3.72 (m, 2H), 4.51 (br s, 1H), 4.73 (br s, 1H), 7.17 (dd, $J = 9$, 3 Hz, 1H), 7.23 (d, $J = 8$ Hz, 2H), 7.28 (d, $J = 9$ Hz, 1H), 7.69 (d, $J = 8$ Hz, 2H), 7.79 ppm (d, $J = 3$ Hz, 1H); MS(DCI/NH_3) *m*/*z* 238/240 $(M + H)^+$; Anal. ($C_{11}H_{14}N_3Cl \cdot C_7H_8SO_3$) C, H, N.

***tert*-Butyl (1*R*,4*R*)-5-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (Boc-10).** Potassium carbonate (16.2 g, 117 mmol) and di-*tert*-butyl dicarbonate (8.1 g, 37 mmol) were added to a solution of (1*R*,4*R*)-2-benzyl-2,5-diazabicylo[2.2.1]heptane dihydrobromide[22] (**10**, 12.4 g, 35.5 mmol) in DMF (100 mL), and the mixture was stirred at ambient temperature for 16 h and then filtered. The filtrate was diluted with water (500 mL), and extracted with Et_2O (3 × 300 mL). The combined extract was washed with brine (10 × 20 mL), dried ($MgSO_4$) and concentrated under vacuum to provide the title compound (9.7 g, 94%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (s, 9H) 1.58−1.68 (m, $J = 11.2$ Hz, 1H) 1.74−1.83 (m, 1H) 2.39−2.48 (m, 1H) 2.71−2.81 (m, 1H) 3.03−3.15 (m, 1H) 3.34−3.44 (m, 2H) 3.67 (s, 2 H), 4.16 (d, $J = 9.2$ Hz, 1H) 7.18−7.34 ppm (m, 5H); MS (DCI/NH_4) *m*/*z* 289 $(M + H)^+$.

***tert*-Butyl (1*R*,4*R*)-2,5-Diazabicyclo[2.2.1]heptane-2-carboxylate (R-9).** A solution of Boc-**10** in ethanol (50 mL) was stirred with 10% Pd/C (150 mg) under H_2 (1 atm) for 16 h. The catalyst was removed by filtration and the solvent was evaporated under vacuum to yield 1.28 g (93%) of the title compound., suitable for use in coupling reactions: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (s, 9H), 1.54 (d, $J = 6$ Hz, 1H), 1.58 (t, $J = 10$ Hz, 1H), 2.70−2.81 (m, 2H), 3.50 (dd, $J = 10$, 2 Hz, 1H), 3.17 (m, 1H), 3.50 (s, 1H), 4.17 (d, $J = 10$ Hz, 1H); MS (DCI/NH_3) *m*/*z* 199 $(M + H)^+$, 216 $(M + NH_4)^+$.

***tert*-Butyl 5-(3-Pyridinyl)-2,5-diazabicylo[2.2.2]octane-2-carboxylate (Boc-13).** 2,5-Diazabicyclo[2.2.2]octane (**12**)[24] (390 mg, 3.5 mmol) was coupled with 3-bromopyridine (545 mg, 3.5 mmol) according to method 'a.' The crude reaction mixture was allowed to cool to ambient temperature, treated with di-*tert*-butyl-dicarbonate (1.5 g, 6.9 mmol) and then allowed to stir an additional 16 h. The reaction mixture was filtered, and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2, hexanes−EtOAc, 9:1−1:1) to provide the title compound (193 mg, 19% yield). MS (DCI/NH_3) *m*/*z* 290 $(M + H)^+$, 307 $(M + NH_4)^+$.

2-(3-Pyridinyl)-2,5-diazabicyclo[2.2.2]octane dihydrochloride (13). A solution of Boc-**13** in ether was treated with excess 1 M HCl in diethyl ether, and the resulting precipitate was filtered to provide the title compound: ^{1}H NMR (300 MHz, CD_3OD) δ 2.04−2.17 (m, 2H), 2.21−2.25 (m, 2H), 3.5−3.69 (m, 3H), 3.90 (d, $J = 12$ Hz, 1H), 4.00 (br s, 1H), 4.45 (br s, 1H), 7.87 (dd, $J = 9$, 5 Hz, 1H), 7.94 (dd, $J = 9$, 1 Hz, 1H), 8.00 (d, $J = 5$ Hz, 1H), 8.28 ppm (d, $J = 2$ Hz, 1H); MS (DCI/NH_3) *m*/*z* 190 $(M + H)^+$, 207 $(M + NH_4)^+$; Anal. ($C_{11}H_{15}N_3 \cdot 2.2\ HCl \cdot 0.3\ C_4H_{10}O$) C, H, N.

Benzyl 2,6-Diazabicyclo[3.2.1]octane-6-carboxylate (15). A solution of benzyl 5-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate[25] (**14**) (2.46 g, 10.0 mmol) in 95% aqueous ethanol (50 mL) was treated with sodium acetate (2.47 g, 30.1 mmol) and hydroxylamine hydrochloride (3.48 g, 50.1 mmol) at ambient temperature. After 45 min, the mixture was concentrated under reduced pressure and the residue was diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with EtOAc (2 × 50 mL). The organic extract was dried ($MgSO_4$) and concentrated to afford a mixture of the desired oximes as a white solid (2.50 g, 96%). A portion of this material (1.57 g, 6.03 mmol) was stirred in 30 mL a 5:1 solution of CH_2Cl_2/trimethylsilylpolyphosphate for 12 h at ambient temperature. The solution was diluted with H_2O (50 mL) and extracted twice with EtOAc (50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; $CH_2Cl_2-CH_3OH$, 95:5) to provide 1.08 g (68%) of benzyl 3-oxo-2,6-diazabicyclo[3.2.1]-octane-6-carboxylate as a white solid. MS (DCI/NH_3) *m*/*z* 261 $(M + H)^+$, 278 $(M + NH_4)^+$. A portion of this material (800 mg, 3.07 mmol) was dissolved in THF (12 mL) and cooled in ice as a 2.0 M solution of borane−methyl sulfide complex in THF (3.4 mL, 6.8 mmol) was added dropwise. The solution was allowed to warm to room temperature, stirred for 14 h, recooled to 0 °C, quenched by the careful addition of CH_3OH (1 mL), and concentrated under reduced pressure. The residue was dissolved in toluene (12 mL) and treated with n-propylamine (1.7 mL). The mixture was stirred for 3 h at 60 °C, cooled to room temperature, and concentrated under reduced pressure. The residue was diluted with saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated. The residue was purified by chromatography (silica gel; $CH_2Cl_2-CH_3OH-{}^cNH_4OH$, 90:10:1) to provide 453 mg (60%) of **15** as a colorless oil. MS (DCI/NH_3) *m*/*z* 247 $(M + H)^+$.

***tert*-Butyl 2,6-Diazabicyclo[3.2.1]octane-2-carboxylate (18).** A solution of benzyl 2,6-diazabicyclo[3.2.1]octane-6-carboxylate (**15**) (140 mg, 0.568 mmol) in CH_2Cl_2 (3 mL) at ambient temperature was treated with triethylamine (0.158 mL, 1.14 mmol) followed by di-*tert*-butyl dicarbonate (136 mg, 0.625 mmol). The solution was stirred for 2 h, diluted with saturated aqueous K_2CO_3 (20 mL), and extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide a colorless oil (190 mg). A suspension of the oil and 10% Pd/C (20 mg) in CH_3OH (10 mL) was stirred under hydrogen (1 atm) for 6 h. The catalyst was removed by filtration through diatomaceous earth (CH_2Cl_2 wash). The filtrate was concentrated to provide the title compound as a colorless oil (106 mg, 91%): MS (DCI/NH_3) *m*/*z* 213 $(M + H)^+$, 230 $M + NH_4)^+$.

2-(6-Chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane Dihydrochloride (17). Prepared from **15** and 2-chloro-5-iodopyridine[66] according to the palladium coupling method 'a' to provide **16** (30% yield) as a light yellow oil. A solution of this material (62 mg, 0.17 mmol) in acetonitrile (3 mL) at 0 °C was treated with

iodotrimethylsilane (37 μL, 0.26 mmol). The solution was stirred at 0 °C for 3 h, quenched with CH_3OH (1 mL)and concentrated under reduced pressure. The residue was diluted with 1 N aqueous HCl (10 mL)and extracted with EtOAc (2 × 10 mL). The aqueous phase was basified with 10% aqueous NaOH (20 mL) and extracted with 3:1 CH_2Cl_2/iPrOH (4 × 10 mL). The extracts were combined, dried (K_2CO_3), and concentrated to provide a light yellow oil. The oil was diluted with EtOH (3 mL) and treated with a solution of HCl in diethyl ether (1 M, 0.17 mL). The resulting precipitate was collected, washed with diethyl ether, and dried under high vacuum to provide the title compound (**17**) as a light yellow solid (31 mg, 60%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.80−2.02 (m, 4H), 3.00 (m, 1H), 3.34−3.40 (m, 2H), 3.60 (m, 1H), 4.15 (m, 1H), 4.68 (m, 1H), 7.33 (d, J = 9 Hz, 1H), 7.43 (dd, J = 9, 3 Hz, 1H), 8.08 ppm (d, J = 3 Hz, 1H); MS (CI/NH_3) m/z 224, 226 $(M + H)^+$; Anal. ($C_{11}H_{14}ClN_3$·2HCl) C, H, N.

6-(6-Chloro-3-pyridinyl)-2,6-diazabicyclo[3.2.1]octane Bis(*p*-toluenesulfonate) (20). Prepared from **18** and 2-chloro-5-iodopyridine[66] according to the palladium coupling method 'a' to provide, after chromatographic purification, a 30% yield of **19** as a light yellow oil. This (40 mg, 0.12 mmol) in EtOAc (3 mL) was treated with *p*-toluenesulfonic acid monohydrate (59 mg, 0.31 mmol). The solution was refluxed for 2 h and allowed to cool to ambient temperature resulting in formation of a precipitate. The precipitate was triturated with diethyl ether (10 mL) and dried under high vacuum to provide 70 mg (85%) of **20** as a white solid. ^{1}H NMR (D_2O) δ 1.92 (m, 1H), 2.14−2.28 (m, 3H), 2.99 (s, 7.5H), 2.99 (dt, J = 6, 13 Hz, 1H), 3.31 (dd, J = 13, 7 Hz, 1H), 3.56 (d, J = 12 Hz, 1H), 3.77 (dd, J = 12, 4 Hz, 1H), 4.38 (m, 2H), 7.25 (dd, J = 9, 3 Hz, 1H), 7.36 (d, J = 8 Hz, 5H), 7.40 (d, J = 9 Hz, 1H), 7.68 (d, J = 8 Hz, 5H), 7.78 ppm (d, J = 3 Hz, 1H); MS (CI/NH_3) m/z 224, 226 $(M + H)^+$; Anal. ($C_{11}H_{14}ClN_3$·2.5$C_7H_8O_3S$·0.5 H_2O) C, H, N.

***tert*-Butyl 2-Azabicyclo[2.2.1]hept-5-en-2-carboxylate (21).** Aqueous formalin (37%, 114 mL, 1.41 mol) was added to a well-stirred solution of NH_4Cl (85.0 g, 1.59 mol) in water (250 mL). Freshly distilled cyclopentadiene (170 g, 2.58 mol) was added all at once, and the mixture was stirred vigorously at ambient temperature for 17 h. The lower, aqueous phase was separated and treated with di-*tert*-butyl dicarbonate (172 g, 0.78 mol). Aqueous 1 M NaOH (100 mL) was added to adjust the pH to ∼8, and the mixture was stirred for 7 h at ambient temperature with addition of solid NaOH (40 g total) to maintain pH ∼ 8. The mixture was extracted with hexanes (2 × 200 mL), and the combined organic phase was washed with brine (50 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was distilled under vacuum to provide the title compound (bp 80−92 °C/10 Torr) as a pale yellow liquid that crystallized on cooling (123 g, 45% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 9H), 1.57 (m, 2H), 2.63 (m, 1H), 3.16 (br s, 1H), 3.31 (dd, J = 9, 3 Hz, 1H), 4.55−4.73 (br m, 1H), 6.25−6.41 ppm (br m, 2H).

***tert*-Butyl 3-Benzyl-3,6-diazabicyclo[3.2.1]octane-6-carboxylate (22).** A stream of ozone (∼5% in O_2) was bubbled through a solution of **21** (0.57 g, 2.92 mmol) in acetic acid (1.5 mL) and CH_2Cl_2 (25 mL) at −78 °C until the solution turned blue. Excess ozone was removed with an oxygen purge (10 min), and dimethyl sulfide (0.54 mL, 7.30 mmol, 2.5 equiv) was added to the solution. The mixture was allowed to warm gradually to 20 °C and stirred for 18 h. The solution was concentrated, and the residue (2.92 g, MS (DCI/NH_3) m/z 228 $(M + H)^+$) was taken up in CH_3OH (15 mL). The solution was cooled in ice, and benzylamine (0.35 mL, 3.21 mmol, 1.1 equiv) and $NaCNBH_3$ (1.83 g, 29.2 mmol, 10 equiv) were added in that order. The ice-bath was removed and the mixture stirred at 20 °C for 24 h. The solution was cooled to 0 °C and diluted with ethyl acetate (10 mL), water (5 mL), and saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was separated and extracted with EtOAc (10 mL). The combined organic extract was washed successively with water (5 mL) and saturated brine (5 mL), dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by chromatography (hexanes−EtOAc, 60:40) to provide **22** as an oil (0.68 g, 2.25 mmol, 77% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 1.37 and 1.51 (s, rotamers, 9H), 1.46 (m, 1H), 1.57 (dd, J = 11, 8 Hz, 1H), 1.88 (m, 1H), 1.97 (m, 1H), 2.32 (m, 2H), 2.82 (m, 1H), 3.02 (m, 1H), 3.52 (m, 3H), 3.91 (m, 1H), 7.20 (m, 1H), 7.27 ppm (m, 4H); MS (DCI/NH_3) m/z 303 $(M + H)^+$.

***tert*-Butyl 3,6-Diazabicyclo[3.2.1]octane-3-carboxylate (24).** A solution of benzyl amine **22** (0.553 g, 1.83 mmol) in CH_3OH (50 mL) was stirred with $Pd(OH)_2$/C (111 mg, 20 wt %) under H_2 (60 psi) at 50 °C for 36 h. The mixture was cooled to 20 °C, filtered through diatomaceous earth, and concentrated to provide **24** as a colorless oil (0.39 g, 100%): ^{1}H NMR (300 MHz, CD_3OD) δ 1.46 and 1.48 (s, rotamers, 9H), 1.78 (dd, J = 12, 5 Hz, 1H), 1.91 (m, 1H), 2.28 (m, 1H), 2.61 (d, J = 13 Hz, 1H), 2.82 (m, 3H), 3.41 (m, 2H), 3.93 ppm (m, 1H); MS (DCI/NH_3) m/z 213 $(M + H)^+$.

***tert*-Butyl 3-(3-Pyridinyl)-3,6-diazabicyclo[3.2.1]octane-6-carboxylate (25).** Prepared in 71% yield from **24** and 3-bromopyridine according to Pd method 'a': ^{1}H NMR (300 MHz, CD_3OD) δ 1.43 and 1.47 (s, rotamers, 9H), 1.81 (dd, J = 12, 6 Hz, 1H), 2.02 (m, 1H), 2.65 (m, 1H), 2.81 (ddd, J = 12, 9, 2 Hz, 1H), 3.03 (m, 1H), 3.23 (m, 1H), 3.43 (m, 1H), 3.72 (m, 1H), 3.84 (m, 1H), 4.22 (m, 1H), 7.25 (m, 2H), 7.89 (m, 1H), 8.11 ppm (d, J = 2 Hz, 1H); MS (DCI/NH_3) m/z 290 $(M + H)^+$.

3-(3-Pyridinyl)- 3,6-diazabicyclo[3.2.1]octane Sesquifumarate (26). A solution of *tert*-butyl 3-(3-pyridinyl)-3,6-diazabicyclo[3.2.1]-octane-6-carboxylate (**25**, 0.25 g, 0.86 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C, and trifluoroacetic acid (3 mL) was added by syringe. The ice-bath was removed and the mixture stirred at 20 °C for 2 h. The solution was concentrated and purified by column chromatography (CH_2Cl_2−CH_3OH−^{c}NH_4OH, 90:10:1) to yield the free base (0.16 g, 0.85 mmol**).** This was dissolved in 10% methanol in diethyl ether (7 mL) and a solution of fumaric acid (0.10 g, 0.86 mmol, 1 equiv) in the same solvent (7 mL). The mixture was stirred for 16 h, and the precipitate was collected by filtration and dried to give 0.169 g of the title compound (0.55 mmol, 64% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 2.08 (m, 2H), 2.85 (m, 1H), 3.01 (br d, J = 12 Hz, 1H), 3.04 (dd, J = 12, 1 Hz, 1H), 3.34 (m, 1H), 3.45 (d, J = 1 Hz, 1H), 3.76 (dd, J = 11, 3 Hz, 1H), 3.88 (dd, J = 12, 4 Hz, 1H), 4.20 (m, 1H), 6.71 (s, 3H), 7.32 (dd, J = 8, 5 Hz, 1H), 7.44 (ddd, J = 9, 3, 1 Hz, 1H), 8.03 (dd, J = 4, 1 Hz, 1H), 8.26 ppm (d, J = 3 Hz, 1H); MS (DCI/NH_3) m/z 190 $(M + H)^+$; Anal. ($C_{11}H_{15}N_3$·1.5 $C_4H_4O_4$) C, H, N.

***tert*-Butyl 3,6-Diazabicyclo[3.2.1]octane-3-carboxylate (27).** Trifluoroacetic acid (3.5 mL) was added to an ice-cooled solution of **22** (0.68 g, 2.25 mmol) in CH_2Cl_2 (7 mL). The ice-bath was removed, and the mixture was stirred at 20 °C for 2 h and then concentrated under vacuum. The residue was taken up in THF (15 mL) and cooled in an ice bath as triethylamine (0.41 mL, 2.92 mmol, 1.3 equiv) was added, followed by trifluoroacetic anhydride (0.38 mL, 2.70 mmol, 1.2 equiv). The mixture was stirred for 15 min at 0 °C and then was allowed to warm to 20 °C. After 18 h, the solution was concentrated, and the residue was purified by chromatography (hexanes−EtOAc, 50:50) to provide the *N*-benzyl-*N*′-trifluoroacetamide as an oil (0.67 g, 2.25 mmol, 100%): ^{1}H NMR (300 MHz, CD_3OD) δ 1.97 (m, 1H), 2.06 (m, 1H), 2.12 (m, 1H), 2.84 (m, 1H), 3.41 (m, 2H), 3.61 (m, 2H), 3.82 (m, 1H), 4.32 (m, 2H), 4.64 (m, 1H), 7.48 ppm (m, 5H); MS (DCI/NH_3) m/z 299 $(M + H)^+$.

This product (0.67 g, 2.25 mmol) was combined with di-(*tert*-butyl) dicarbonate (0.55 g, 2.51 mmol, 1.1 equiv) and 20% $Pd(OH)_2$/C (135 mg) in methanol (50 mL). The solution was stirred under a hydrogen atmosphere (60 psi) for 18 h, filtered through diatomaceous earth, and concentrated under vacuum. The residue was taken up in methanol (10 mL) and water (2 mL), and powdered K_2CO_3 (0.5 g, 3.62 mmol, 1.6 equiv) was added. The mixture was stirred for 20 h and then concentrated. The residue was taken up in a mixture of CH_2Cl_2−CH_3OH−^{c}NH_4OH (90:10:1) and filtered through layers of diatomaceous earth and silica gel. The filtrate was concentrated to provide *tert*-butyl 3,6-diazabicyclo[3.2.1]-octane-3-carboxylate (**27**) (0.47 g, 2.21 mmol, 98% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 1.42 (m, 1H), 1.46 (s, 9H), 1.89 (m, 2H), 2.58 (m, 1H), 3.00 (m, 2H), 3.12 (m, 2H), 3.78 (m, 1H), 3.84 (dd,

J = 13, 3 Hz, 1H), 3.92 ppm (br d, J = 14 Hz, 1H); MS (DCI/NH_3) m/z 213 $(M + H)^+$.

***tert*-Butyl 6-(3-Pyridinyl)-3,6-diazabicyclo[3.2.1]octane-2-carboxylate (28).** Prepared in 54% yield from **27** and 3-bromopyridine according to the Pd-mediated method 'a' described above: ^{1}H NMR (CH_3OH-d_4, 300 MHz) δ 1.09 (s, 9H), 1.95 (m, 1H), 2.09 (m, 1H), 2.59 (m, 1H), 2.90 (d, J = 13 Hz, 1H), 2.98 (d, J = 13 Hz, 1H), 3.08 (d, J = 9 Hz, 1H), 3.50 (dd, J = 9, 6 Hz, 1H), 3.95 and 4.17 (m, 1H), 4.07 (m, 1H), 4.33 (dt, J = 13, 1 Hz, 1H), 7.04 (ddd, J = 8, 3, 1 Hz, 1H), 7.22 (dd, J = 8, 5 Hz, 1H), 7.78 (d, J = 4 Hz, 1H), 7.90 pm (d, J = 3 Hz, 1H); MS (DCI/NH_3) m/z 290 $(M + H)^+$.

6-(3-Pyridinyl)-3,6-diazabicyclo[3.2.1]octane Fumarate (29). Trifluoroacetic acid (3 mL) was added to an ice-cooled solution of **28** (0.215 g, 0.74 mmol) in CH_2Cl_2 (5 mL). The ice-bath was removed, and the mixture was stirred at 20 °C for 2 h. The solution was concentrated and purified by column chromatography (silica, CH_2Cl_2−CH_3OH−$^cNH_4OH$, 90:10:1) to yield 0.14 g of the free base as an oil (0.74 mmol, 100% yield). This was taken up in 10% methanol in diethyl ether (7 mL) and treated with a solution of fumaric acid (86 mg, 0.74 mmol, 1 equiv) in the same solvent (7 mL).The mixture was stirred for 16 h, and then the precipitate was filtered and dried to provide the title compound (168 mg, 74% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 2.10 (m, 2H), 2.82 (m, 1H), 3.19 (d, J = 13 Hz, 1H), 3.33 (m, 2H), 3.45 (m, 1H), 3.48 (d, J = 10 Hz, 1H), 3.59 (dd, J = 10, 5 Hz, 1H), 4.37 (dd, J = 5, 4 Hz, 1H), 6.68 (s, 2.6 H), 7.15 (ddd, J = 8, 3, 1 Hz, 1H), 7.28 (dd, J = 8, 5 Hz, 1H), 7.88 (d, J = 5 Hz, 1H), 8.00 ppm (d, J = 3, 1H); MS (DCI/NH_3) m/z 190 $(M + H)^+$; Anal. ($C_{11}H_{15}N_3$·1.3 $C_4H_4O_4$): C, H, N.

(1*R*,4*R*)-2-(6-Chloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (R-8). Prepared from (1*R*,4*R*)-*tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**R-9**) according to the procedure for **S-8**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.93 (d, J = 11 Hz, 1H), 2.14 (d, J = 11 Hz, 1H), 2.29 (s, 3H), 3.13−3.31 (m, 3H), 3.61 (dd, J = 11, 2 Hz, 1H), 4.48 (s, 1H), 4.68 (s, 1H), 7.13 (d, J = 8 Hz, 2H), 7.17 (dd, J = 8, 3 Hz, 1H), 7.31 (d, J = 9 Hz, 1H), 7.49 (d, J = 8 Hz, 2H), 7.85 ppm (d, J = 3 Hz, 1H); MS (DCI/NH_3) m/z 210 $(M + H)^+$; Anal. ($C_{10}H_{12}N_3Cl$·$C_7H_8SO_3$): C, H, N.

(1*S*,4*S*)-2-(2-Pyridinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-30). A solution of *tert*-butyl (1*S*,4*S*)-5-(5-bromopyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (from the preparation of Boc-**S-8**, 110 mg, 0.31 mmol) in ethyl acetate (30 mL) was stirred with 10% Pd−C (30 mg) under H_2 (1 atm) for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated to a brownish solid. This was taken up in CH_2Cl_2 (3 mL), and trifluoroacetic acid (1 mL) was added. After 30 min, the yellow solution was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2−CH_3OH−$^cNH_4OH$, 90:10:1) to provide **S-30** (19 mg, 36% yield) as the free base. This was combined with *p*-toluenesulfonic acid monohydrate (20 mg) in ethyl acetate (6 mL) and ethanol (1 mL). The mixture was warmed to dissolve solids. On cooling to 0 °C, the salt crystallizes as a white solid (25 mg, 24% overall): ^{1}H NMR (300 MHz, CD_3OD) δ 2.02 (br d, J = 11 Hz, 1H), 2.23 (br d, J = 11 Hz, 1H), 2.37 (s, 3H), 3.35 (m, 2H), 3.50 (br d, J = 10 Hz, 1H), 3.71 (dd, J = 10, 2 Hz, 1H), 4.44 (br s, 1H), 4.90 (br s, 1H), 6.60 (d, J = 8 Hz, 1H), 6.70 (dd, J = 7, 5 Hz, 1H), 7.21 (d, J = 8 Hz, 2H), 7.59 (ddd, J = 8, 7, 2 Hz, 1H), 7.69, (d, J = 8 Hz, 2H), 8.08 (br d, J = 5 Hz, 1 H); MS(DCI/NH_3) m/z 176 $(M + H)^+$; Anal. ($C_{10}H_{13}N_3$·$C_7H_8SO_3$·0.5 H_2O) C, H, N.

(1*S*,4*S*)-2-(4-Pyridinyl)-2,5-diazabicyclo[2.2.1]heptane Bis(trifluoroacetate) (S-32). A solution of 4-bromopyridine hydrochloride (500 mg, 2.57 mmol) in 20% K_2CO_3 (aq, 10 mL) was extracted with CH_2Cl_2 (20 mL). The extract was dried ($MgSO_4$) and concentrated by distillation at atmospheric pressure to leave 4-bromopyridine as a yellow oil. This was combined with **S-9** (400 mg, 2.02 mmol), $Pd_2(dba)_3$ (37 mg, 0.04 mmol), and *rac*-BINAP (50 mg, 0.08 mmol) in toluene 20 mL), and Cs_2CO_3 (1.04 g, 3.2 mmol) was added. The mixture was heated under nitrogen at 80 °C for 40 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (30 mL), and filtered through a pad of diatomaceous earth. The yellow filtrate was concentrated under vacuum, and the residue was purified by chromatography (CH_2Cl_2−CH_3OH−$^cNH_4OH$, 90:10:1) to provide *tert*-butyl (1*S*,4*S*)-5-(4-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a pale yellow oil (170 mg, 31%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 and 1.46 (s, 9H, Boc rotomers), 1.99 (m, 2H), 3.22−3.55 (m, 4H), 4.49 (br s, 1H), 4.57 and 4.71 (br s, 1H), 6.43 (br d, J = 7 Hz, 2H), 8.21 (br d, J = 7 Hz, 2H); MS (DCI/NH_3) m/z 276 $(M + H)^+$.

A solution of this intermediate (110 mg, 0.40 mmol) in CH_2Cl_2 (2 mL) was cooled in ice as trifluoroacetic acid (1 mL) was added. The solution was allowed to warm to room temperature over 90 min, and the volatiles were removed under vacuum. The residue was triturated with 10% CH_3OH−ether (5 mL) and filtered to provide **S-32** as a golden-yellow solid (133 mg, 82% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 2.20 (br d, J = 12 Hz, 1H), 2.34 (br d, J = 12 Hz, 1H), 3.46 (m, 2H), 3.35 (s, 2H), 3.70 (dd, J = 12, 2 Hz, 1H), 3.86 (dd, J = 12, 2 Hz, 1H), 4.68 (br s, 1H), 5.12 (br s, 1H), 7.02 (very br, 2H), 8.23 (d, J = 7 Hz, 2H); MS(DCI/NH_3) m/z 176 $(M + H)^+$; Anal. ($C_{10}H_{13}N_3$·$2C_2HO_2F_3$) C, H, N.

(1*S*,4*S*)-2-(6-Fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-36). A modification of Pd-coupling method 'a' was used: A solution of (**S-9**) (0.300 g, 1.01 mmol) in anhydrous toluene (30 mL) was treated with 2-fluoro-5-iodopyridine[66] (0.34 g, 1.52 mmol), $Pd_2(dba)_3$ (0.028 g, 0.03 mmol), (*S*)-(−)-2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl (0.028 g, 0.06 mmol), and sodium *tert*-butoxide (0.248 g, 2.58 mmol). The reaction mixture was heated at 80 °C for 5 h, cooled to room temperature, diluted with diethyl ether (100 mL), washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography (CH_2Cl_2−CH_3OH, 97:3) to provide Boc-**S-36** (0.095 g, 21% yield) as a yellow oil. This was heated with *p*-toluenesulfonic acid as described for (**S-8**) to provide the title salt (**S-36**): ^{1}H NMR (300 MHz, CD_3OD) δ 2.06 (d, J = 12 Hz, 1H), 2.29 (d, J = 12 Hz, 1H), 2.36 (s, 6H), 3.28(m, 1H). 3.35 (s, 2H), 3.74 (dd, J = 12, 3 Hz, 1H), 4.51 (m, 1H), 4.68 (br s, 1H), 6.96 (dd, J = 9, 3 Hz, 1H), 7.23 (d, J = 8 Hz, 2H), 7.30 (m, 1H), 7.55 (m, 1H), 7.69 ppm (d, J = 8 Hz, 2H); MS (DCI/NH_3) m/z 194 $(M + H)^+$; Anal. ($C_{10}H_{12}N_3F$·$C_7H_8SO_3$) C, H, N.

(1*R*,4*R*)-2-(6-Fluoro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (R-36). Prepared from **R-9** according to the procedures for **S-36**: ^{1}H NMR (free base, 300 MHz, $CDCl_3$) δ 1.75 (d, J = 12 Hz, 1H), 1.96 (d, J = 12 Hz, 1H), 2.92 (d, J = 9 Hz, 1H), 3.07 (s, 2H), 3.66 (dd, J = 9, 3 Hz, 1H), 3.81 (s, 1H), 4.26 (s, 1H), 6.78 (dd, J = 6, 1 Hz, 1H), 6.92−7.0 (m, 1H), 7.45 ppm (t, J = 1 Hz, 1H); MS (DCI/NH_3) m/z 194 $(M + H)^+$, 211 $(M + NH_4)^+$; Anal. ($C_{10}H_{12}N_3F$· $C_7H_8SO_3$·0.2 H_2O) C, H, N.

(1*S*,4*S*)-2-(3-Pyridinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-31). Prepared in 65% yield from **S-9** and 3-bromopyridine according to coupling method 'a' followed by deprotection and salt formation with *p*-toluenesulfonic acid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.09 (d, J = 11 Hz, 1H), 2.30 (d, J = 11 Hz, 1H), 2.36 (s, 3H), 3.36 (m, 3H), 3.76 (dd, J = 11, 2 Hz, 1H), 4.52 (s, 1H), 4.74 (s, 1H), 7.15 (ddd, J = 8, 3, 1 Hz, 1H), 7.22 (d, J = 8 Hz, 2H), 7.29 (dd, J = 8, 5 Hz, 1H), 7.70 (d, J = 8 Hz, 2H), 7.94 (dd, J = 5, 1 Hz, 1H), 7.99 ppm (d, J = 3 Hz, 1H); MS (DCI/NH_3) m/z 176 $(M + H)^+$, 193 $(M + NH_4)^+$; Anal. ($C_{10}H_{13}N_3$· $C_7H_8O_3S$) C, H, N.

(1*R*,4*R*)-2-(3-Pyridinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (R-31). Prepared as for **S-31**, but starting with **R-9**: ^{1}H NMR (free base, $CDCl_3$, 300 MHz) δ 1.85 (d, J = 12 Hz, 1H), 1.95 (d, J = 12 Hz, 1H), 2.98 (d, J = 9 Hz, 1H), 3.08 (s, 2H), 3.63 (dd, J = 10, 3 Hz, 1H), 3.82 (s, 1H), 4.32 (s, 1H), 6.78−6.84 (m, 1H), 7.08−7.15 (m, 1H), 7.95 (dd, J = 8, 2 Hz, 1H), 8.00 (d, J = 3 Hz, 1H); MS (DCI/NH_3) m/z 176 $(M + H)^+$; Anal. ($C_{10}H_{13}N_3$·$C_7H_8O_3S$·0.5 H_2O) C, H, N.

(1*S*,4*S*)-2-(6-Methyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-37). Prepared in 54% yield from

5-bromo-2-methylpyridine and **S-9** by coupling procedure 'a,' followed by deprotection/salt formation with *p*-toluenesulfonic acid: ^{1}H NMR (free base, $CDCl_3$, 300 MHz) δ 1.84 (d, $J = 9$ Hz, 1H), 1.93 (d, $J = 9$ Hz, 1H), 2.42 (s, 3H), 2.92 (d, $J = 7$ Hz, 1H), 3.03−3.10 (m, 2H), 3.65 (dd, $J = 6$, 2 Hz, 1H), 3.78 (s, 1H), 4.28 (s, 1H), 6.78 (dd, $J = 7$, 4 Hz, 1H), 6.97 (d, $J = 4$ Hz,1H), 7.85 (d, $J = 2$ Hz, 1H); MS (DCI/NH_3) *m*/*z* 190 $(M + H)^+$; Anal. ($C_{11}H_{15}N_3 \cdot C_7H_8O_3S$) C, H, N.

(1*R*,4*R*)-2-(6-Methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluenesulfonate (R-38). Prepared in 32% yield from 5-bromo-2-methoxypyridine and **R-9** according to coupling method 'a,' followed by deprotection/salt formation with *p*-toluenesulfonic acid: ^{1}H NMR (free base, 300 MHz, CD_3OD) δ 2.05 (d, $J = 11$ Hz, 1H), 2.28 (d, $J = 11$ Hz, 1H), 3.25 (dd, $J = 12$, 3 Hz, 1H), 3.35 (s, 2H), 3.72 (dd, $J = 12$, 3 Hz, 1H), 3.78 (s, 3H), 4.48 (t, $J = 1$ Hz, 1H), 4.61 (s, 1H), 6.84 (d, $J = 11$ Hz, 1H), 7.28 (dd, $J = 9$, 3 Hz, 1H), 7.53 (d, $J = 3$ Hz, 1H); MS (DCI/NH_3) *m*/*z* 206 $(M + H)^+$; Anal. ($C_{11}H_{15}N_3O \cdot C_7H_8O_3S$) C, H, N.

(*S*,*S*)-2-(6-Aminopyridin-3-yl)-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluenesulfonate (S-40). Palladium on carbon (10%, 11 mg) was added to a solution of **S-39** (38 mg, 0.10 mmol) in methanol (5 mL), and the mixture was stirred at room temperature under hydrogen (1 atm) for 6 h. The reaction mixture was filtered through diatomaceous earth under nitrogen, and the filtrate was concentrated under vacuum. The residue was crystallized from 95% ethanol (5 mL) to provide the title salt as an off-white solid (25 mg, 70%): ^{1}H NMR (300 MHz, CD_3OD) δ 1.99 (d, $J = 12$ Hz, 1H), 2.26 (d, $J = 12$ Hz, 1H), 2.37 (s, 3H), 3.15 (dd, $J = 10$, 1 Hz, 1H), 3.22−3.39 (m, 2H), 3.68 (dd, $J = 11$, 2 Hz, 1H), 4.40 (br. s, 1H), 4.52 (br. s,1H), 6.63 (d, $J = 9$ Hz, 1H), 7.08 (dd, $J = 9$, 3 Hz, 1H), 7.23 (d, $J = 8$ Hz, 2H), 7.39 (d, $J = 3$ Hz, 1H), 7.70 ppm (d, $J = 8$ Hz, 2H); MS (DCI/NH_3) *m*/*z* 191$(M + H)^+$; Anal. ($C_{10}H_{14}N_4 \cdot C_7H_8O_3S$) C, H, N.

***tert*-Butyl (1*S*,4*S*)-5-(5-Cyano-3-pyridinyl)-2,5-diazabicyclo-[2.2.1]heptane-2-carboxylate (Boc-S-41).** Prepared in 66% overall yield from **S-9** and 3-bromo-5-cyanopyridine according to coupling procedure 'a' to provide Boc-**S-41** as an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 and 1.46 (br. s, 9 H), 1.85−2.14 (m, 2H), 3.21−3.48 (m, 3 H), 3.59 (d, $J = 8$ Hz, 1H), 4.43 (s, 1H), 4.57 and 4.71 (br. s, 1H), 6.89−7.01 (m, 1H), 8.07−8.15 (m, 1H), 8.20 ppm (s, 1H); MS (DCI/NH_3) *m*/*z* 301 $(M + H)^+$.

(1*S*,4*S*)-2-(5-Cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluensulfonate (S-41). Boc-**S-41** (300 mg, 1 mmol) was dissolved in ethyl acetate (15 mL) at reflux. A solution of *p*-toluenesulfonic acid monohydrate (195 mg, 1.03 mmol) in ethyl acetate (10 mL) was added, and the reaction mix was heated at reflux for 8 h, by which time a precipitate had formed. The mixture was filtered, and the solid was recrystallized from 95% ethanol to provide **S-41** as a white solid (220 mg, 60%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.11 (d, $J = 11$ Hz, 1H), 2.30 (d, $J = 11$ Hz, 1H), 2.37 (s, 3H), 3.38 (m, 3H), 3.77 (dd, $J = 11$, 3 Hz, 1H), 4.57 (m, 1H), 4.82 (br s, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.47 (dd, $J = 3$, 1 Hz, 1H), 7.69 (d, $J = 8$ Hz, 2H), 8.23 (d, $J = 1$ Hz, 1H), 8.25 ppm (d, $J = 3$ Hz, 1H).; MS (DCI/NH_3) *m*/*z* 200 $(M + H)^+$; Anal. ($C_{11}H_{12}N_4 \cdot C_7H_8O_3S$) C, H, N.

(1*R*,4*R*)-2-(5-Cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluensulfonate (R-41). Prepared from **R-9** according to the procedures for **S-41**: ^{1}H NMR (free base, 300 MHz, CD_3OD) δ 2.10 (d, $J = 11$ Hz, 1H), 2.31 (d $J = 11$ Hz, 1H), 3.38 (d, $J = 2$ Hz, 2H), 3.42 (d, $J = 1$ Hz, 1H), 3.75 (dd, $J = 9$, 3 Hz, 1H), 4.56 (s, 1H), 4.82 (s, 1H), 7.50 (dd, $J = 4$, 1 Hz, 1H), 8.23 (d, $J = 4$ Hz, 1H), 8.25 ppm (d, $J = 3$ Hz, 1H); MS (DCI/NH_3) *m*/*z* 201 $(M + H)^+$, 218 $(M + NH_4)^+$. Anal. ($C_{11}H_{12}N_4 \cdot C_7H_8O_3S \cdot 0.5H_2O$) C, H, N.

(1*S*,4*S*)-2-(5-Aminomethyl-3-pyridinyl)-2,5-diazabicyclo[2.2.1]-heptane Tris(trifluoroacetate) (S-42). A solution of Boc-**S-41** (0.267 g, 0.89 mmol) in 30% NH_3/methanol (30 mL) was agitated with Raney-Nickel (0.10 g) in a Parr shaker under hydrogen (60 psi) for 4 h. The mixture was filtered and concentrated under vacuum. The residue was purified by chromatography (CH_2Cl_2−CH_3OH−$^cNH_4OH$ 90:10:1) to provide a white solid (0.199 g, 73% yield). This was taken up in CH_2Cl_2 (5 mL) and stirred with trifluoroacetic acid (2.5 mL). After 1 h, the mixture was concentrated under vacuum and triturated with 10% methanol−ether to provide the title compound as a white solid (298 mg, 54% from Boc-**S-41**): ^{1}H NMR (300 MHz, CD_3OD) δ 2.14 (d, $J = 12$ Hz, 1H), 2.32 (d, $J = 12$ Hz, 1H), 3.36−3.48 (m, 2H), 3.49 (d, $J = 11$ Hz, 1H), 3.78 (dd, $J = 11$, 2 Hz, 1H), 4.20 (s, 2H), 4.60 (s, 1H), 4.78−4.84 (m, 1H), 7.49 (s, 1H), 8.08 (s, 1H), 8.15 ppm (d, $J = 2$ Hz, 1H); MS (DCI/NH_3) *m*/*z* 205 $(M + H)^+$; Anal. ($C_{11}H_{16}N_4 \cdot 3C_2HO_2F_3$) C, H, N.

(1*S*,4*S*)-2-[5-Hydroxy-3-pyridinyl]-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluenesulfonate (S-43). Coupling of **S-9** and 3-(benzyloxy)-5-bromopyridine[66] according to method 'a' provided an off-white solid in 60% yield. This product (0.50 g, 1.31 mmol) was dissolved in EtOH (15 mL) and treated with 10% Pd/C (0.02 g) under hydrogen (1 atm) at 40 °C for 6 h. The reaction mixture was allowed to cool to ambient temperature, and the catalyst was removed by filtration. The filtrate was diluted with diethyl ether (125 mL), washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography (CH_2Cl_2:CH_3OH, 95:5) to provide the debenzylated material as a yellow oil (90%: MS (DCI/NH_3) *m*/*z* 292 $(M + H)^+$). Deprotection/salt formation with *p*-toluenesulfonic acid provided the title salt (48%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.07 (d, $J = 12$ Hz, 1H), 2.28(d, $J = 13$ Hz, 1H), 2.36 (s, 4.5 H), 3.32−3.42 (m, 3H), 3.71 (dd, $J = 10$, 4 Hz, 1H), 4.51 (s, 1H), 4.68 (s, 1H), 6.62 (t, $J = 2$ Hz, 1H), 7.21 (d, $J = 8$ Hz, 3H), 7.51−7.56 (m, 2H), 7.69 ppm (d, $J = 8$ Hz, 3H); MS (DCI/NH_3) *m*/*z* 192 $(M + H)^+$; Anal. ($C_{10}H_{13}N_3O \cdot 1.5\ C_7H_8O_3S \cdot 2.4\ H_2O$) C,H,N.

(1*R*,4*R*)-2-[5-Hydroxy-3-pyridinyl]-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluenesulfonate (R-43). Prepared in 30% overall yield from **R-9** and 3-(benzyloxy)-5-bromopyridine[66] as described above for **S-43**. The salt (**R-43**) was obtained as an off-white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.05 (d, $J = 13$ Hz, 1H), 2.28 (d, $J = 13$ Hz, 1H), 2.37 (s, 3H), 3.32−3.36 (m, 3H), 3.70 (dd, $J = 10$, 3 Hz, 1H), 4.51 (s, 1H), 4.67 (s, 1H), 6.55 (t, $J = 2$ Hz, 1H), 7.21 (d, $J = 8$ Hz, 2H), 7.51 (d, $J = 2$ Hz, 1H), 7.53 (d, $J = 2$ Hz, 1H), 7.69 ppm (d, $J = 8$ Hz, 2H); MS (DCI/NH_3) *m*/*z* 192 $(M + H)^+$; Anal. ($C_{10}H_{13}N_3O \cdot C_7H_8O_3S \cdot 0.8\ H_2O$): C, H, N.

(1*S*,4*S*)-2-(6-Chloro-5-hydroxy-3-pyridinyl)-2,5-diazabicyclo-[2.2.1]heptane *p*-Toluenesulfonate S-44). Coupling of **S-9** and 5-bromo-2-chloro-3-(methoxymethoxy)-pyridine according to palladium method 'a' provided *tert*-butyl (1*S*,4*S*)-5-(6-chloro-5-methoxymethoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (Boc-**S-44**) in 44% yield. A solution of this material (1.00 g, 2.7 mmol) in EtOH (2.0 mL) was treated with 4 N HCl/dioxane (5 mL) and then heated at 60 °C for 4 h. The reaction mixture was allowed to cool to ambient temperature and then concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2−CH_3OH−$^cNH_4OH$, 90:10:1) to provide the titled free base (0.424 g) as a light yellow solid. This was warmed with *p*-toluenesulfonic acid monohydrate (0.356 g, 1 equiv) in 95% EtOH (3 mL) for 10 min, and the mixture was concentrated under vacuum to produce the title compound (0.78 g, 72% yield) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.08 (d, $J = 12$ Hz, 1H), 2.28 (d, $J = 12$ Hz, 1H), 2.37 (s, 3H), 3.32−3.38 (m, 3H), 3.70 (dd, $J = 12$, 3 Hz, 1H), 4.52 (t, $J = 1$ Hz, 1H), 4.65 (s, 1H), 6.64 (d, $J = 3$ Hz, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.32 (d, $J = 3$ Hz, 1H), 7.66 ppm (d, $J = 8$ Hz, 2H); MS (DCI/NH_3) *m*/*z* 226 $(M + H)^+$, 243 $(M + NH_4)^+$; Anal. ($C_{10}H_{12}N_3ClO \cdot C_7H_8O_3S \cdot 3.0\ H_2O$) C, H, N.

(1*R*,4*R*)-2-(6-Chloro-5-hydroxy-3-pyridinyl)-2,5-diazabicyclo-[2.2.1]heptane *p*-Toluenesulfonate (R-44). 5-Bromo-2-chloro-3-(methoxymethoxy)pyridine was coupled with **R-9** according to the procedure for method 'a' to produce *tert*-butyl (1*R*,4*R*)-5-(6-chloro-5-methoxymethoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (Boc-**R-44**) in 52% yield after purification by column chromatography (5% CH_3OH− CH_2Cl_2). A solution of this material (0.60 g, 1.62 mmol) in acetonitrile (8 mL) was shaken at room temperature with acid resin (Amberlyst 15, 7.5 g) for 48 h. The resin was removed by filtration, and the filtrate was concentrated

under vacuum. The residue was purified by column chromatography ($CH_2Cl_2-CH_3OH-^cNH_4OH$, 90:10:1) to provide the titled free base (0.121 g) as a white solid. This was heated in EtOH with *p*-toluenesulfonic acid monohydrate (0.102 g, 1 equiv) for 10 min. The solvent was removed under reduced pressure and the residue triturated with EtOAc (5 mL) to provide the title salt (222 mg, 33% yield) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.06 (d, $J = 12$ Hz, 1H), 2.36 (s, 3.6H), 2.37 (d, $J = 12$ Hz, 1H), 3.28−3.35 (m, 3H), 3.70 (dd, $J = 12$, 3 Hz, 1H), 4.51 (s, 1H), 4.65 (s, 1H), 6.65 (d, $J = 3$ Hz, 1H), 7.22 (d, $J = 8$ Hz, 2.4H), 7.35 (d, $J = 3$ Hz, 1H), 7.68 ppm (d, $J = 8$ Hz, 2.4H); MS (DCI/NH_3) *m/z* 226 $(M + H)^+$, 243 $(M + NH_4)^+$; Anal. ($C_{10}H_{12}N_3OCl \cdot 1.2\ C_7H_8O_3S \cdot 0.60\ H_2O$) C, H, N.

(1*S*,4*S*)-2-(5-Methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane Bis(*p*-toluenesulfonate) (S-45). Prepared in 38% yield from **S-9** and 3-bromo-5-methoxypyridine according to coupling method 'a,' followed by deprotection/salt formation with *p*-toluenesulfonic acid: ^{1}H NMR (free base, 300 MHz, $CDCl_3$) δ 1.82−2.01 (m, 2H), 3.02 (d, $J = 10$ Hz, 1H), 3.05−3.10 (m, 2H), 3.63 (dd, $J = 9$, 3 Hz, 1H), 3.82 (s, 3H), 3.87 (s, 1H), 4.32 (s, 1H), 6.33 (t, $J = 2$ Hz, 1H), 7.64 (d, $J = 3$ Hz, 1H), 7.68 ppm (d, $J = 2$ Hz, 1H); MS (DCI/NH_3) *m/z* 206 $(M + H)^+$; Anal. ($C_{11}H_{15}N_3O \cdot 2C_7H_8O_3S \cdot H_2O$) C, H, N.

(1*R*,4*R*)-2-(5-Methoxy-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (R-45). Prepared in 35% yield from **R-9** and 3-bromo-5-methoxypyridine as for **S-45**: ^{1}H NMR (300 MHz, CD_3OD) δ 2.08 (d, $J = 11$ Hz, 1H), 2.30 (dd, $J = 11$, 1 Hz, 1H), 2.36 (s, 3H), 3.33−3.40 (m, 3H), 3.75 (dd, $J = 11$, 3 Hz, 1H), 3.85 (s, 3H), 4.48−4.57 (m, 1H), 4.74 (s, 1H), 6.68 (t, $J = 2$ Hz, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.60 (d, $J = 2$ Hz, 1H), 7.66 (d, $J = 2$ Hz, 1H), 7.67−7.73 ppm (m, 2H); MS (DCI/NH_3) *m/z* 206 $(M + H)^+$; Anal. ($C_{11}H_{15}N_3O \cdot C_7H_8O_3S \cdot 0.2H_2O$) C, H, N.

(1*R*,4*R*)-2-(6-Chloro-5-methyl-3-pyridinyl)-2,5-diazabicyclo-[2.2.1]heptane *p*-Toluenesulfonate (R-46). Prepared from **R-9** and 2-chloro-5-iodo-3-methylpyridine[66] according to coupling procedure 'a' and deprotection/salt formation with *p*-toluenesulfonic acid: ^{1}H NMR (free base, 300 MHz, $CDCl_3$) δ 1.89 (d, $J = 10$ Hz, 1H), 1.98 (d, $J = 10$ Hz, 1H), 2.31 (s, 3H), 3.00 (dd, $J = 10$, 1 Hz, 1H), 3.09 (s, 2H), 3.63 (dd, $J = 9$, 3 Hz, 1H), 3.88 (s, 1H), 4.29 (s, 1H), 6.72 (d, $J = 2$ Hz, 1H), 7.56 ppm (d, $J = 3$ Hz, 1H); MS (DCI/NH_3) *m/z* 224 $(M + H)^+$; Anal. ($C_{11}H_{14}N_3Cl \cdot C_7H_8O_3S$): C, H, N.

(1*R*,4*R*)-2-(5-Trifluoromethyl-3-pyridinyl)-2,5-diazabicyclo-[2.2.1]heptane *p*-Toluenesulfonate (R-47). Prepared in 45% yield from **R-9** and 3-chloro-5-(trifluoromethyl)pyridine by coupling method 'a' followed by deprotection and salt formation with *p*-toluenesulfonic acid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.07 (d, $J = 11$ Hz, 1H), 2.27 (d, $J = 11$ Hz, 1H), 2.36 (s, 3H), 3.33−3.48 (m, 2H), 3.50−3.67 (m, 1H), 3.65−3.87 (m, 1H), 4.54 (s, 1H), 5.07 (s, 1H), 6.69 (d, $J = 9$ Hz, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.69 (d, $J = 8$ Hz, 2H), 7.78 (dd, $J = 9$, 2 Hz, 1H), 8.36 ppm (s, 1H); MS (DCI/NH_3) *m/z* 244 $(M + H)^+$; Anal. ($C_{11}H_{12}N_3F_3 \cdot C_7H_8O_3S$) C, H, N.

(1*R*,4*R*)-2-(5,6-Dichloro-3-pyridinyl)-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluenesulfonate (R-48). Prepared in 55% yield from **R-9** and 2,3-dichloro-5-iodopyridine[66] according to coupling method 'a' and deprotection/salt formation with *p*-toluenesulfonic acid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.07 (d, $J = 11$ Hz, 1H), 2.29 (d, $J = 11$ Hz, 1H), 2.36 (s, 3H), 3.32−3.45 (m, 3H), 3.73 (dd, $J = 11$, 3 Hz, 1H), 4.40−4.59 (m, 1H), 4.74 (s, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.35 (d, $J = 3$ Hz, 1H), 7.69 (d, $J = 8$ Hz, 2H), 7.77 ppm (d, $J = 3$ Hz, 1H); MS (DCI/NH_3) *m/z* 244 $(M + H)^+$; Anal. ($C_{10}H_{11}N_3Cl_2 \cdot C_7H_8O_3S$) C, H, N.

(1*R*,4*R*)-2-(6-Chloro-5-methoxy-3-pyridinyl)-2,5-diazabicyclo-[2.2.1]heptane *p*-Toluenesulfonate (R-49). Prepared in 37% overall yield from **R-9** and 5-bromo-2-chloro-3-methoxypyridine according to coupling method 'a,' followed by deprotection/salt formation with *p*-toluenesulfonic acid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.07 (d, $J = 11$ Hz, 1H), 2.30 (d, $J = 10$ Hz, 1H), 2.36 (s, 3H), 3.30 (m, 1H under solvent), 3.33−3.40 (m, 2H), 3.75 (dd, $J = 11$, 2 Hz, 1H), 3.91 (s, 3H), 4.53 (s, 1H), 4.75 (s, 1H), 6.77 (d, $J = 3$ Hz, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.35 (d, $J = 2$ Hz, 1H), 7.68 ppm (d, $J = 8$ Hz, 2H); MS (DCI/NH_3) *m/z* 240 $(M + H)^+$; Anal. ($C_{11}H_{14}N_3OCl \cdot C_7H_8O_3S$) C, H, N.

(1*S*,4*S*)-2-(5-Aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo-[2.2.1]heptane Bis(trifluoroacetate) (S-50). A solution of *tert*-butyl (1*S*,4*S*)-5-(5-cyano-3-pyridinyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (Boc-**S-41**, 0.37 g, 1.43 mmol) in ethanol (15 mL) was treated with 30% H_2O_2 (1.1 mL) and 25% NaOH (1.1 mL), and the mixture was stirred at room temperature for 2 h. The volatiles were removed under vacuum, and the residue was purified by chromatography (silica, $CH_2Cl_2-CH_3OH$ 95:5) to provide Boc-**S-50** as an off-white solid (217 mg, 55%). This product (40 mg) was stirred in dichloromethane (1 mL), and trifluoroacetic acid (0.5 mL) was added. The amber solution was stirred at room temperature for 2 h and then concentrated under vacuum. The residue was triturated with ether (2 mL) to produce an off-white solid that was isolated by filtration and dried under vacuum (42 mg, 75%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.12 (d, $J = 12$ Hz, 1H), 2.32 (d, $J = 12$ Hz, 1H), 3.41−3.59 (m, 3H), 3.81 (dd, $J = 11$, 2 Hz, 1H), 4.59 (s, 1H), 4.89 (s, 1H), 7.61−7.77 (m, 1H), 8.21 (br. s, 1H), 8.44 ppm (br. s, 1H); MS (DCI/NH_3) *m/z* 219 $(M + H)^+$; Anal. ($C_{11}H_{13}N_4O \cdot 2\ C_2HO_2F_3$) C, H, N.

(1*R*,4*R*)-2-(5-Aminocarbonyl-3-pyridinyl)-2,5-diazabicyclo-[2.2.1]heptane Bis(trifluoroacetate) (R-50). Prepared analogueously to **S-50**, beginning with Boc-**R-41**: ^{1}H NMR (300 MHz, CD_3OD) δ 2.14 (d, $J = 12$ Hz, 1H), 2.33 (d, $J = 12$ Hz, 1H), 3.4−3.6 (m, 3H), 3.81 (dd, $J = 11$, 2 Hz, 1H), 4.57 (s, 1H), 4.90 (s, 1H), 7.6−7.8 (m, 1H), 8.24 (br. s, 1H), 8.45 ppm (br. s, 1H); MS (DCI/NH_3) *m/z* 219 $(M + H)^+$; Anal. ($C_{11}H_{13}N_4O \cdot 2\ C_2HO_2F_3$) C, H, N.

(1*S*,4*S*)-2-(3-Pyridazinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-51). A solution of **S-9** (342 mg, 1.7 mmol) in anhydrous toluene (8.5 mL) was heated with 3,6-dichloropyridazine (256 mg, 1.7 mmol) and triethylamine (0.24 mL, 170 mg, 1.7 mmol) for 16 h at 110 °C. The mixture was cooled to room temperature and concentrated under reduced pressure, and the residue was purified by chromatography (silica gel, $CH_2Cl_2-CH_3OH-^cNH_4OH$, 95:5:1 eluent) to provide a white solid (432 mg, 81% yield). This material was dissolved in methanol (7 mL) containing triethylamine (0.27 mL) and then shaken with 10% Pd/C (10 mg) under hydrogen (60 psi) at 50 °C for 1.3 h. The catalyst was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by chromatography (silica gel, $CH_2Cl_2-CH_3OH$, 95:5 eluent) to provide a white solid (0.35 g, 92%). This was combined with *p*-toluenesulfonic acid monohydrate (265 mg, 1.1 equiv) in EtOAc (5 mL) and heated at reflux for 6 h. The resulting precipitate was collected by filtration and recrystallized from ethanol to provide the title salt: ^{1}H NMR (300 MHz, CD_3OD) δ 2.09 (d, $J = 12$ Hz, 1H), 2.31 (d, $J = 11$ Hz, 1H), 2.36 (s, 3H), 3.33−3.46 (m, 2H), 3.54−3.70 (m, 1H), 3.79 (dd, $J = 11$, 3 Hz, 1H), 4.55 (s, 1H), 5.07 (s, 1H), 7.07 (dd, $J = 9$, 1 Hz, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.47 (dd, $J = 9$, 4 Hz, 1H), 7.70 (d, $J = 8$ Hz, 2H), 8.46−8.60 ppm (m, 1H); MS (DCI/NH_3) *m/z* 177 $(M + H)^+$; Anal. ($C_9H_{12}N_4 \cdot C_7H_8O_3S \cdot 0.2\ H_2O$) C, H, N.

(1*S*,4*S*)-2-(6-Chloro-5-methyl-3-pyridazinyl)-2,5-diazabicyclo-[2.2.1]heptane Bis(*p*-toluenesulfonate) (S-52). 3,6-Dichloro-4-methylpyridazine was reacted with **S-9** according to coupling method 'b' (56%), followed by deprotection/salt formation with *p*-toluenesulfonic acid (81% yield) to provide the title compound: ^{1}H NMR (free base, 300 MHz, $CDCl_3$) δ 1.84 (d, $J = 10$ Hz, 1H), 1.96 (d, $J = 10$ Hz,1H), 2.32 (s, 3H), 2.92−3.02 (m, 2H), 3.36 (s, 1H), 3.58 (dd, $J = 10$, 2 Hz, 1H), 3.83 (s, 1H), 4.76−4.88 (m, 1H), 6.94 ppm (s, 1H); MS (DCI/NH_3) *m/z* 225 $(M + H)^+$, 242 $(M + NH_4)^+$; Anal. ($C_{10}H_{13}N_4Cl \cdot 2C_7H_8O_3S$) C, H, N.

(**1*R*,4*R*)-2-(6-Chloropyridazin-3-yl)-2,5-diazabicyclo[2.2.1]-heptane Bis(*p*-toluenesulfonate) (R-11).** Prepared from **R-9** and 3,6-dichloropyridazine according to coupling procedure 'b.' Deprotection and salt formation with *p*-toluenesulfonic acid provided the title salt (94% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.96 (d, $J = 10$ Hz, 1H), 2.17 (d, $J = 10$ Hz, 1H), 2.29 (s, 6H), 3.24−3.28 (m, 2H), 3.56−3.67 (m, 2H), 4.53 (s, 1H), 4.95 (s, 1H), 7.11 (d, $J = 8$ Hz, 4H), 7.21 (d, $J = 9$ Hz, 1H), 7.49 (d, $J = 8$ Hz, 4H), 7.62

ppm (d, $J = 9$ Hz, 1H); MS (DCI/NH_3) m/z 211 $(M + H)^+$; Anal.-($C_9H_{11}N_4Cl \cdot 2C_7H_8O_3S$) C, H, N.

(1*S*,4*S*)-2-(4-Chloro-1-phthalazinyl)-2,5-diazabicyclo[2.2.1]-heptane Bis(*p*-toluenesulfonate) (S-53). 1,4-Dichlorophthalazine was coupled to **S-9** according to method 'a' (62%) followed by deprotection/salt formation with *p*-toluenesulfonic acid to provide the title salt (83% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 2.23 (d, $J = 12$ Hz, 1H), 2.36 (s, 6H), 2.45−2.53 (m, 1H), 3.51−3.60 (m, 1H), 3.91 (dd, $J = 12$, 2 Hz, 1H), 4.06 (dd, $J = 11$, 2 Hz, 1H), 4.52 (dd, $J = 11$, 3 Hz, 1H), 4.65−4.71 (m, 1H), 5.27 (s, 1H), 7.20 (d, $J = 8$ Hz, 4H), 7.64 (d, $J = 8$ Hz, 4H), 8.07−8.22 (m, 2H), 8.36−8.42 ppm (m, 2H); MS (DCI/NH_3) m/z 261$(M + H)^+$; Anal. ($C_{13}H_{13}N_4Cl \cdot 2\ C_7H_8O_3S$) C, H, N.

(1*S*,4*S*)-2-(5-Pyrimidinyl)-2,5-diazabicyclo[2.2.1]-heptanetrifluoroacetate (S-54). Prepared from **S-9** and 5-bromopyrimidine according to coupling method 'a' (91%) followed by deprotection/salt formation with trifluoroacetic acid to provide the title compound after trituration with 10% methanol in ether (45%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.10 (d, $J = 11$ Hz, 1 H), 2.31 (d, $J = 12$ Hz, 1 H), 3.28−3.33 (m, 2H), 3.35−3.44 (m, 1 H), 3.77 (dd, $J = 11$, 3 Hz, 1 H), 4.57 (t, $J = 2$ Hz, 1 H), 4.81−4.84 (m, 1 H), 8.27 (s, 2H), 8.55 ppm (s, 1 H); MS (DCI/NH_3) m/z 177 $(M + H)^+$; Anal. ($C_9H_{12}N_4 \cdot C_2HO_2F_3 \cdot 0.1\ H_2O$) C, H, N.

(1*S*,4*S*)-2-(6-Chloro-1,3-pyrimidin-4-yl)-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluenesulfonate (S-55). Prepared in 10% yield from **S-9** and 4,6-dichloropyrimidine according to coupling procedure 'a,' followed by deprotection/salt formation with *p*-toluenesulfonic acid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.06−2.16 (m, 1H), 2.20−2.33 (m, 1H), 2.37 (s, 3H), 3.35−3.49 (m, 2H), 3.64−3.83 (m, 2H), 4.60 (s, 1H), 5.19 (br.s, 1H), 6.75 (br. s, 1H), 7.23 (d, $J = 8$ Hz, 2H), 7.68 (d, $J = 8$ Hz, 2H), 8.40 ppm (s, 1H); MS (DCI/NH_3) m/z 211/213 $(M + H)^+$; Anal. $C_9H_{11}N_4Cl \cdot C_7H_8O_3S \cdot H_2O$) C, H, N.

(1*S*,4*S*)-2-(Phenyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-56). Prepared in 75% yield from **S-9** and bromobenzene using coupling procedure 'a' (97%) followed by deprotection/salt formation with *p*-toluenesulfonic acid to provide the title salt (76%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.03 (d, $J = 11$ Hz, 1H), 2.29 (d, $J = 11$ Hz, 1H), 2.36 (s, 3H), 3.23−3.41 (m, 3H), 3.73 (dd, $J = 11$, 2 Hz, 1H), 4.39−4.51 (m, 1H), 4.64 (s, 1H), 6.67 (d, $J = 8$ Hz, 2H), 6.75 (t, $J = 8$ Hz, 1H), 7.17−7.26 (m, 4H), 7.70 ppm (d, $J = 8$ Hz, 2H); MS (DCI/NH_3) m/z 175; Anal. ($C_{11}H_{14}N_2 \cdot C_7H_8O_3S \cdot 0.2H_2O$) C, H, N.

(1*S*,4*S*)-2-(4-Nitrophenyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-57). Coupling of *p*-bromonitrobenzene with **S-9** according to method 'a' (50%), followed by deprotection/salt formation with *p*-toluenesulfonic acid provided the title salt (78%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.10 (d, $J = 12$ Hz, 1H), 2.32 (d, $J = 12$ Hz, 1H), 2.36 (s, 3H), 3.33−3.44 (m, 2H), 3.48 (dd, $J = 11$, 1 Hz, 1H), 3.79 (dd, $J = 11$, 2 Hz, 1H), 4.57 (s, 1H), 4.85−4.93 (m, 1H), 6.70−6.79 (m, 2H), 7.22 (d, $J = 8$ Hz, 2H), 7.69 (d, $J = 8$ Hz, 2H), 8.06−8.20 ppm (m, 2H); MS (DCI/NH_3) m/z 220 $(M + H)^+$; Anal. ($C_{11}H_{13}N_3O_2 \cdot C_7H_8O_3S$) C, H, N.

(1*S*,4*S*)-2-(3-Nitrophenyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-58). Coupling of **S-9** with 3-bromonitrobenzene according to method 'a,' followed by deprotection/salt formation with *p*-toluenesulfonic acid in EtOAc, provided the title salt as a golden-yellow crystalline powder in 77% overall yield: ^{1}H NMR (300 MHz, CD_3OD) δ 2.08 (d, $J = 11$ Hz, 1H), 2.32 (d, $J = 11$ Hz, 1H), 2.36 (s, 3H), 3.33−3.43 (m, 3H), 3.79 (dd, $J = 11$, 3 Hz, 1H), 4.50−4.55 (m, 1H), 4.79 (s, 1H), 7.06 (dd, $J = 8$, 2 Hz, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.41−7.49 (m, 2H), 7.58 (dd, $J = 8$, 2 Hz, 1H), 7.69 ppm (d, $J = 8$ Hz, 2H); MS (DCI/NH_3) m/z 220 $(M + H)$. Anal. ($C_{11}H_{13}N_3O_2 \cdot C_7H_8O_3S$) C, H, N.

(1*S*,4*S*)-2-(3-Fluorophenyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-59). Prepared from **S-9** and 3-bromofluorobenzene according to coupling method 'a' (87%), followed by deprotection/salt formation with *p*-toluenesulfonic acid to provide the title salt, which was purified by recrystallization from ethanol after treatment with decolorizing carbon (27%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.05 (d, $J = 12$ Hz, 1H), 2.29 (d, $J = 12$ Hz, 1H), 2.36 (s, 3H), 3.20−3.28 (m, 1H), 3.33−3.37 (m, 2H), 3.71 (dd, $J = 11$, 3 Hz, 1H), 4.48 (t, $J = 2$ Hz, 1H), 4.64 (s, 1H), 6.38−6.49 (m, 3H), 7.16−7.22 (m, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.70 ppm (d, $J = 8$ Hz, 2H) MS (ESI) m/z 193 $(M + H)$. Anal. ($C_{11}H_{13}N_2F \cdot C_7H_8O_3S$) C, H, N.

(1*S*,4*S*)-2-(4-Chlorophenyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-60). Prepared from *p*-bromochlorobenzene and **S-9** according to procedure 'a' (32%), followed by deprotection/salt formation with *p*-toluenesulfonic acid to provide the title salt as a pale violet, crystalline solid (83%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.02 (d, $J = 11$ Hz, 1H), 2.28 (d, $J = 11$ Hz, 1H), 2.37 (s, 3H), 3.25 (dd, $J = 11$, 1 Hz, 1H), 3.31−3.37 (m, 2H), 3.71 (dd, $J = 11$, 3 Hz, 1H), 4.41−4.48 (m, 1H), 4.62 (s, 1H), 6.62−6.67 (m, 2H), 7.17−7.22 (m, 2H), 7.22 (d, $J = 8$ Hz, 2H), 7.68−7.71 ppm (m, 2H); MS (DCI/NH_3) m/z 209/211 $(M + H)^+$; Anal. ($C_{11}H_{13}N_2Cl \cdot C_7H_8O_3S$) C, H, N.

(1*S*,4*S*)-2-(3-Methylisothiazol-5-yl)-2,5-diazabicyclo[2.2.1]-heptane *p*-Toluenesulfonate (S-61). Prepared in 3% overall yield from 5-bromo-3-methylisothiazole[67] and **S-9** according to coupling method 'a,' followed by deprotection with *p*-toluenesulfonic acid: ^{1}H NMR (300 MHz, CD_3OD) δ 2.14 (d, $J = 11$ Hz, 1H), 2.27 (s, 3H), 2.38 (s, 3H), 2.64 (d, $J = 11$ Hz, 1H), 3.11−3.18 (m, 2H), 3.23 (dd, $J = 11$, 2 Hz, 1H), 3.59 (dd, $J = 10$, 2 Hz, 1H), 4.13 (s, 1H), 4.26 (s, 1H), 6.08 (s, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.71 ppm (d, $J = 8$ Hz, 2H); MS (ESI) m/z 196 $(M + H)$. Anal. ($C_9H_{13}N_3S \cdot C_7H_8O_3S$) C, H, N.

(1*R*,4*R*)-2-(3-Methyl-(1,2,4)-thiadiazol-5-yl)-2,5-diazabicyclo-[2.2.1]heptane Trifluoroacetate (R-62). Prepared from **R-9** (40 mg, 0.20 mmol) and 5-chloro-3-methyl-[1,2,4]thiadiazole[68] (26 mg, 0.22 mmol) according to Pd-coupling method 'a,' followed by deprotection with Amberlyst resin and purification by HPLC (0.1% trifluoroacetic acid/water−acetonitrile eluent) to provide the title salt: ^{1}H NMR (500 MHz, CD_3OD) δ 2.12 (d, $J = 11$ Hz, 1H), 2.31−2.40 (m, 4H), 3.39−3.50 (m, 2H), 3.57 (d, $J = 11$ Hz, 1H), 3.77 (dd, $J = 11$, 2 Hz, 1H), 4.60 (s, 1H), 4.75 ppm (s, 1H); MS (ESI) m/z 197 $(M + H)$.

(1*S*,4*S*)-2-(2-Thiazolyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-63). Prepared from **S-9** (40 mg, 0.20 mmol) and 2-bromothiazole (32.8 mg, 0.2 mmol) according to thermal coupling method 'b' (35%) followed by deprotection with *p*-toluenesulfonic acid in EtOAc to provide the title compound (50%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.11 (d, $J = 12$ Hz, 1H), 2.34 (d, $J = 12$ Hz, 1H), 2.36 (s, 6H), 3.37−3.56 (m, 2H), 3.61 (dd, $J = 11$, 1 Hz, 1H), 3.80 (dd, $J = 11$, 3 Hz, 1H), 4.59 (s, 1H), 4.76 (s, 1H), 7.23 (d, $J = 4$ Hz, 1H), 7.23 (d, $J = 8$ Hz, 4H), 7.25 (d, $J = 4$ Hz, 1H), 7.69 ppm (d, $J = 8$ Hz, 4H); MS (DCI/NH_3) m/z 182 $(M + H)^+$; Anal. ($C_8H_{11}N_3S \cdot 2\ C_7H_8O_3S$) C, H, N.

(1*S*,4*S*)-2-(3-Quinolinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-64). Prepared from **S-9** and 3-bromoquinoline by coupling method 'a' followed by deprotection with TFA/CH_2Cl_2. The crude TFA salt was eluted through a silica gel column with $CH_2Cl_2-CH_3OH-{}^cNH_4OH$ (90:10:1) to provide the free base (65% from **S-9**). This was combined with *p*-toluenesulfonic acid and crystallized from EtOAc−EtOH (1:1) to provide the title salt (72%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.13 (d, $J = 11$ Hz, 1H), 2.35 (s, 3H), 2.39 (d, $J = 11$ Hz, 1H), 3.43 (s, 2H), 3.49 (d, $J = 11$ Hz, 1H), 3.90 (dd, $J = 11$, 3 Hz, 1H), 4.57 (s, 1H), 4.91 (s, 1H), 7.21 (d, $J = 8$ Hz, 2H), 7.40 (d, $J = 3$ Hz, 1H), 7.43−7.55 (m, 2H), 7.69 (d, $J = 8$ Hz, 2H), 7.72−7.80 (m, 1H), 7.82−7.96 (m, 1H), 8.53 (d, $J = 3$ Hz, 1H); MS (DCI/NH_3) m/z 226 $(M + H)^+$; Anal. ($C_{14}H_{15}N_3 \cdot C_7H_8O_3S$) C, H, N.

(1*S*,4*S*)-2-(2-Quinolinyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesulfonate (S-65). Prepared from **S-9** and 2-chloroquinoline by coupling method 'b,' followed by deprotection with TFA/CH_2Cl_2. The crude material was purified by flash chromatography on silica gel, eluting with $CH_2Cl_2-CH_3OH-{}^cNH_4OH$ (90:10:1) to provide the free base, which was combined with *p*-toluenesulfonic acid and crystallized from EtOAc−EtOH (5:1) to provide the title salt as an off-white, crystalline solid (46% overall): ^{1}H NMR (300 MHz, CD_3OD) δ 2.09 (d, $J = 11$ Hz, 1H), 2.26−2.37 (m, 1H), 2.36 (s, 3H), 3.44 (s, 2H), 3.69−3.77 (m, 1H), 3.83−3.91 (m, 1H),

4.55 (s, 1H), 5.17 (s, 1H), 6.93 (d, $J = 9$ Hz, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.23−7.30 (m, 1H), 7.49−7.61 (m, 1H), 7.63−7.77 (m, 4H), 8.06 ppm (d, $J = 9$ Hz, 1H); MS (DCI/NH_3) *m/z* 226 (M + H)$^+$; Anal. ($C_{14}H_{15}N_3 \cdot C_7H_8O_3S \cdot 0.2\ H_2O$) C, H, N.

(1*R*,4*R*)-3-(2,5-Diazabicyclo[2.2.1]hept-2-yl)-thieno[3,2-*b*]pyridine Tris(*p*-toluenesulfonate) (R-66). Prepared from **R-9** and 3-bromothieno[3,2-*b*]pyridine[69] according to coupling procedure 'a,' followed by deprotection with TFA/CH_2Cl_2. The resulting material was purified by flash chromatography on silica gel, eluting with CH_2Cl_2−CH_3OH−$^cNH_4OH$ (90:10:1) to provide the free base, which was combined with *p*-toluenesulfonic acid in isopropyl acetate to provide the title salt: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.90 (d, $J = 11$ Hz, 1H), 2.15 (d, $J = 11$ Hz, 1H), 2.29 (s, 9 H), 3.15−3.37 (m, 2H), 3.57 (d, $J = 11$ Hz, 1H), 3.84 (d, $J = 11$ Hz, 1H), 4.43 (d, $J = 2$ Hz, 1H), 5.27 (s, 1H), 6.75 (s, 1H), 7.11 (d, $J = 8$ Hz, 6H), 7.38 (dd, $J = 8$, 5 Hz, 1H), 7.47 (d, $J = 8$ Hz, 6H), 8.40 (dd, $J = 8$, 2 Hz, 1H), 8.62 ppm (dd, $J = 4$, 2 Hz, 1H); MS (DCI/NH_3) *m/z* 232 (M + H)$^+$; Anal. ($C_{12}H_{13}N_3S \cdot 3\ C_7H_8O_3S \cdot 1.6\ H_2O$) C, H, N.

(1*R*,4*R*)-2-(2,5-Diazabicyclo[2.2.1]hept-2-yl)-thieno[3,2-*b*]pyridine Bis(*p*-toluenesulfonate) (R-67). Prepared in 6% yield from **R-9** and 2-iodo-thieno[3,2-*b*]pyridine[69] according to coupling procedure 'a,' followed by deprotection with TFA/CH_2Cl_2. The product was purified by flash chromatography on silica gel, eluting with CH_2Cl_2−CH_3OH−$^cNH_4OH$ (90:10:1), and the resulting free base was combined with *p*-toluenesulfonic acid to provide the title salt after trituration with EtOAc: ^{1}H NMR (300 MHz, CD_3OD) 2.20 (d, $J = 12$ Hz, 1H), 2.36 (s, 6H), 2.39−2.50 (m, 1H), 3.44−3.59 (m, 2H), 3.71 (dd, $J = 11$, 1 Hz, 1H), 3.90 (dd, $J = 11$, 2 Hz, 1H), 4.69 (s, 1H), 4.87 (s, 1H), 6.43 (s, 1H), 7.21 (d, $J = 8$ Hz, 4H), 7.32 (dd, $J = 8$, 6 Hz, 1H), 7.69 (d, $J = 8$ Hz, 4H), 8.32 (dd, $J = 6$, 1 Hz, 1H), 8.54 (d, $J = 8$ Hz, 1H); MS (DCI/NH_3 232 (M + H)$^+$; Anal. ($C_{12}H_{13}N_3S \cdot 2\ C_7H_8O_3S$) C, H, N.

(1*R*,4*R*)-2-(3-Pyridinylmethyl)-2,5-diazabicyclo[2.2.1]heptane Trihydrobromide (R-69). A solution of ((2*R*,4*S*)-1-[(4-methylphenyl)sulfonyl]-4-{[(4-methylphenyl)sulfonyl]oxy}-pyrrolidinyl)methyl *p*-toluenesulfonate[22] (1.5 g, 2.6 mmol) and 3-(aminomethyl)pyridine (1.0 g, 9.3 mmol) in toluene (20 mL) was heated at reflux for 16 h. The mixture was cooled and filtered, and the filter cake was washed with toluene (20 mL). The combined wash and filtrate was concentrated under reduced pressure, and the residue was purified by chromatography (hexanes:EtOAc, 9:1 to 1:1) to provide the tosyl-protected amine (410 mg, 46%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (d, $J = 8$ Hz, 1H), 1.62 (d, $J = 10$ Hz, 1H), 2.42 (s, 3H), 2.44 (m, 1H), 2.66 (dd, $J = 10$, 2 Hz, 1H), 2.99 (dd, $J = 10$, 2 Hz, 1H), 3.39−3.48 (m, 2H), 3.62−3.41 (d, $J = 10$ Hz, 1H), 4.23 (br s, 1H), 4.35 (t, $J = 5$ Hz, 1H), 7.31 (m, 1H), 7.43−7.46 (m, 2H), 7.62 (m, 1H), 7.71−7.74 (m, 2H), 8.31−8.43 ppm (m, 2H).

This toluenesulfonamide (320 mg, 0.9 mmol) was combined with acetic acid (3.4 mL) and 33% HBr/acetic acid (7 mL), and the mixture was heated at 70 °C for 18 h. The mixture was cooled to room temperature, and the precipitate was filtered, washed with ether, and dried. The solid was recrystallized from EtOH/EtOAc to provide **R-69** (332 mg, 80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.22 (m, 1H), 2.47 (m, 1H), 3.29−3.48 (m, 2H), 3.35 (m, 1H), 3.69 (m, 1H), 4.19−4.53 (m, 2H), 5.59 (m, 2H), 8.05 (m, 1H), 8.62 (m, 1H), 8.78−8.88 ppm (m, 2H); MS (DCl/NH_3) *m/z* 190 (M + H)$^+$; Anal. ($C_{11}H_{15}N_3 \cdot 3.0\ HBr \cdot 0.1\ H_2O$) C, H, N.

(1*R*,4*R*)-2-(5-Bromo-6-chloropyridine-3-sulfonyl)-2,5-diazabicyclo[2.2.1]heptane *p*-Toluenesufonate (R-70). Solid **R-9** (66 mg, 0,.33 mol) was added to a solution of 5-bromo-6-chloropyridine-3-sulfonyl chloride (102 mg, 0.35 mol) in CH_2Cl_2 (3 mL). Triethylamine (0.3 mL, 2 mmol) was added, and the solution was allowed to stand at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 (15 mL) and washed successively with 5% H_2SO_4 (7 mL) and 20% K_2CO_3 (7 mL). The organic phase was dried (Na_2SO_4) and concentrated to an off-white solid (150 mg, 99%). This was combined with *p*-toluenesulfonic acid (monohydrate, 62 mg, 1 equiv) in EtOAc (20 mL), and the resulting solution was heated at reflux for 4 h. The mixture was cooled to room temperature and concentrated under vacuum, and the residue was crystallized from EtOAc−EtOH (5:1) to provide the title salt (98 mg, 60%): ^{1}H NMR (300 MHz, CD_3OD) δ 1.69 (d, $J = 12$ Hz, 1H), 1.86 (d, $J = 12$ Hz, 1H), 2.27−2.46 (m, 3H), 3.36−3.65 (m, 4H), 4.41 (s, 1H), 4.68−4.79 (m, 1H), 7.23 (d, $J = 8$ Hz, 2H), 7.62−7.77 (m, 2H), 8.61 (d, $J = 2$ Hz, 1H), 8.83 ppm (d, $J = 2$ Hz, 1H); MS (DCI/NH_3) m/z352/354/356 (M + H)$^+$; Anal. ($C_{10}H_{11}N_3O_2SClBr \cdot C_7H_8O_3S$) C, H, N.

(1*R*,4*R*)-2-(6-Chloropyridine-3-carbonyl)-2,5-diazabicyclo-[2.2.1]heptane *p*-Toluenesufonate (R-71). A mixture of 6-chloronicotinic acid (880 mg, 5.6 mmol) and **R-9** (990 mg, 5.0 mmol) was suspended in toluene (25 mL), and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroisoquinoline (EEDQ, 1.62 g, 6.5 mmol) was added. The mixture was stirred for 16 h at room temperature and then concentrated under vacuum, and the residue was purified by chromatography on silica gel (hexanes−EtOAc, 50:50) to provide a colorless gum (992 mg, 59%). A portion (480 mg, 1.42 mmol) was taken up in EtOAc (10 mL), and *p*-toluenesulfonic acid monohydrate (857 mg, 4.5 mmol) was added. The mixture was heated at 70 °C for 3 h, cooled to room temperature, and filtered to provide the title salt (428 mg, 73%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (d, $J = 13$ Hz, 1H), 2.28 (s, 3H), 2.36−2.43 (m, 1H), 2.79−2.93 (m, 1H), 3.53−3.72 (m, 3H), 4.42 (s, 1H), 4.96 (s, 1H), 7.05−7.17 (m, 2H), 7.24 (d, $J = 10$ Hz, 1H), 7.47 (d, $J = 8$ Hz, 2H), 7.63 (d, $J = 9$ Hz, 1H), 9.47 ppm (br. s, 1H); MS (DCI/NH_3) *m/z* 238/240 (M + H)$^+$; Anal. ($C_{11}H_{12}N_3OCl \cdot C_7H_8O_3S$) C,H,N.

(1*S*,4*S*)-2-(6-Chloropyridin-3-yl)-2,5-diazabicyclo[2.2.1]-heptanone *p*-Toluenesulfonate (S-72). A suspension of N-Boc-*trans*-4-hydroxy-L-proline (1.10 g, 4.8 mmol, Aldrich), 5-amino-2-chloropyridine (0.67 g, 5.2 mmol), and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroisoquinoline (EEDQ, 1.54 g, 6.2 mmol) in toluene (15 mL) was stirred at room temperature under nitrogen for 16 h. The mixture was concentrated under vacuum and the residue purified by chromatography (silica, CH_2Cl_2−CH_3OH, 95:5). The partially purified amide (1.21 g, 3.5 mmol) was dissolved in THF (15 mL), and triphenylphosphine (2.79 g, 10.6 mmol) and diethyl azodicarboxylate (DEAD, 1.12 mL, 7.1 mmol) were added in succession. The mixture was stirred at room temperature for 16 h and then concentrated under vacuum. The residue was passed through a silica column CH_2Cl_2−CH_3OH, 95:5) to provide the bicyclic lactam as a colorless oil (0.52 g, 46%). A portion (150 mg, 0.43 mmol) was dissolved in (5 mL), and 4 M HCl/dioxane (1 mL) was added at room temperature. After 1 h, the mixture was concentrated under vacuum, and the residue was purified by chromatography (silica, CH_2Cl_2−CH_3OH−$^cNH_4OH$, 90:10:1). The free base was combined with *p*-toluenesulfonic acid in EtOAc to provide the salt as a hygroscopic gum (72 mg, 39%): ^{1}H NMR (300 MHz, CD_3OD) δ 2.18 (d, $J = 11$ Hz, 1H), 2.37 (s, 3H), 2.59 (d, $J = 11$ Hz, 1H), 3.42−3.53 (m, 1H), 3.58−3.69 (m, 1H), 4.54 (s, 1H), 5.17 (s, 1H), 7.23 (d, $J = 8$ Hz, 2H), 7.51 (d, $J = 8$ Hz, 1H), 7.70 (d, $J = 8$ Hz, 2H), 8.11 (dd, $J = 8$, 3 Hz, 1H), 8.68 ppm (d, $J = 3$ Hz, 1H); DCI/NH_3 *m/z* 224/226 (M + H)$^+$.

In Vitro Biological Assays. [^{3}H]-Cytisine Binding.[27] Rat cerebral cortical membranes were purchased from ABS Inc. (Wilmington, DE). Prior to use, the frozen membrane pellets were slowly thawed, washed, resuspended in 20 volumes of buffer (containing: 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$, and 50 mM Tris-Cl, pH 7.4 at 4 °C). After centrifuging at 20 000*g* for 15 min, the pellets were resuspended in 30 volumes of buffer.

Test compounds were dissolved in water to make 10 mM stock solutions. Each solution was then diluted (1:100) with buffer (as above) and further taken through serial log dilutions to produce test solutions covering a 6-log range in concentration around the IC_{50}.

Homogenate (containing 125−150 μg protein) was added to triplicate tubes containing the range of test compound concentrations and [^{3}H]-cytisine (1.25 nM, 30 Ci/mmol)) in a final volume of 500 μL. Samples were incubated for 60 min at 4 °C and then rapidly filtered through Whatman GF/B filters presoaked in 0.5% poly-

ethyleneimine using 3 × 4 mL of ice-cold buffer. The filters are counted in 4 mL of Ecolume (ICN). Nonspecific binding was determined in the presence of 10 μM (−)-nicotine. The IC_{50} value was determined with the RS-1 (BBN) nonlinear least-squares curve-fitting program, and the IC_{50} value was converted to a K_i value using the Cheng and Prusoff correction ($K_i = IC_{50}/(1 + [\text{ligand}]/K_d$ of ligand). Data reported in Tables 1−4 represent averages of at least three independent determinations.

Agonist Activity in IMR-32 Cells. The assay was performed according to the reported procedure[39] except that Fluo-4 (Molecular Probes, Eugene, OR) was used as the calcium-chelating dye and a buffer composed of (HEPES buffer, 20 mM HEPES, 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 5 mM glucose, 500 mM atropine, and 5 mM $CaCl_2$) was used for washing and the assay dilutions. Test compounds were evaluated in duplicate, each at 10 half-log concentration increments. EC_{50} values were determined by fitting the data to a sigmoidal logistic equation using the software Prism (Graph Pad, San Diego, CA). The data in Tables 1 and 2 represent an average of at least two independent EC_{50} determinations.

Rat Striatal Dopamine Release. Dopamine release from rat striatal tissue was assessed using the 96-well method developed in our laboratory.[29] Concentration−response data were collected at serial log dilutions of the test compound, and the results in Table 2 represent an average of at least three independent determinations.

In Vivo Pharmacology. Hot Box in Rat. The hot box method has been described in detail elsewhere.[70] Briefly, the rat was placed in the hot box on a glass surface at 30 °C for 30 min prior to a baseline measure of a response to thermal stimulation of the hind paws using the focused beam from a projector lamp. The rat was dosed with saline or test compound (ip) and returned to the chamber. The latency to withdrawal of the stimulated paw was measured at 15, 30, and 45 min after dosing. Six rats were used in each dose group. For clarity, response times were averaged across time for statistical analysis.

Formalin Test in Rat. This method has been described in detail elsewhere.[70] Test compounds were dosed (ip) 5 min prior to administration (sc) of formalin (50 μL of 5% formalin in saline) into the dorsal aspect of one of the rear paws. Effects of the test compounds were evaluated in the time interval 30−50 min following administration of formalin (Phase 2 response). The number of flinches was recorded as a measure of persistent pain for 6−8 rats per dose group. Significant differences between drug and saline responses were determined at a 95% confidence level.

Spinal Nerve Ligation in Rat. This model[65] is a test for neuropathic allodynia that develops over several days following tight ligation of the L5 and L6 spinal nerves. The rats' responses to mechanical stimulation were measured using von Frey filaments. Rats exhibiting allodynia (defined as a withdrawal threshold ≤4 g) were used in this study. Rats were dosed (ip) with test compound or saline, and the withdrawal threshold measured at 15, 30, 60, and 120 min following the dose. Average responses for six animals per dose were collapsed across time to produce the data in Figure 3.

Supporting Information Available: Data for antagonist blockade of the antinociceptive effect of **8S-b**, brain-plasma distribution data for **8R-k**, and details for determination of enantiomeric purity for **S-9** and **R-9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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